Evidence Report/Technology Assessment

Number 126

Effects of Soy on Health Outcomes

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. This report was requested and funded by the National Center for Complementary and Alternative Medicine (NCCAM) and the Office of Dietary Supplements, National Institutes of Health. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome comments on this evidence report. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to **epc@ahrq.gov**.

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Structured Abstract

Context. Soy products, including both protein and isoflavones, have been touted for a number of clinical benefits related to a putative estrogen-like effect. However, potential risks of chronic soy consumption are also of concern.

Objectives. Systematic review to describe the range of soy products and outcomes that have been studied, to summarize the effects of soy consumption to prevent a wide variety of medical conditions in healthy adults, and to summarize adverse events related to soy consumption.

Data Sources. We searched MEDLINE®, EMBASE, and the Commonwealth Agricultural Bureau (CAB) databases. Additional studies were identified in bibliographies of selected reviews and by technical experts.

Study Selection. English-language, prospective studies of soy products in adults, of at least 4 weeks' duration were included. We reviewed outcomes related to cardiovascular health, menopausal symptoms and reproductive health, endocrine function, tumor-related biomarkers, bone health, neurocognitive health, kidney function, and glucose metabolism. Eligibility criteria were adjusted for several outcomes.

Data Extraction. Selected studies were extracted for study design, demographics, amount of soy product, soy protein, and isoflavones, control, outcomes. Based on these data, studies were graded for quality and applicability.

Data Synthesis. We screened almost 4,800 abstracts and retrieved 599 full text articles, of which 178 were eligible for review. Soy supplements (including soy milk) were used in about three quarters of all the trials analyzed in this report, with soy foods used in the remainder of the trials. Most used soy protein with isoflavones, one-third used isoflavones alone, and a few used soy protein without isoflavones. Textured soy protein and soy flour were the most common soy foods investigated. Among studies with soy protein, the range of soy protein consumed daily was 14 to 154 g, with a median of 36 g per day (equivalent to over a pound of tofu daily). Among studies with soy isoflavones, the range of isoflavones consumed daily was 10 to 185 mg, with a median of 80 mg per day. These ranges were the same for all lipid profile studies. There is a large degree of heterogeneity among the studies in terms of soy products evaluated, soy protein and isoflavone doses, study durations, background diet, controls used, and study design. No study evaluated clinical cardiovascular events. Meta-analysis indicates that consumption of soy products appears to exert a small benefit on low density lipoprotein (LDL) – the summary net change was –5 (95% confidence interval [CI] –8 to –3) mg/dL – and on triglycerides – net change –8 (95% CI –11, –5) mg/dL. No significant effect was seen on high density lipoprotein (HDL) – net change +0.6 (95% CI –0.5, +1.8). Across studies, there is the possible suggestion that higher doses of soy protein are associated with greater LDL reduction among those with elevated baseline LDL, but not with HDL or triglycerides. Dose of isoflavones was not associated with effect for any lipid. Higher baseline LDL or triglycerides may also be associated with net effect for these 2 lipids; the effect of baseline HDL is unclear. In individual studies, the effect of dose and baseline was generally inconsistent. Meta-analysis of blood pressure (BP) found no effect of soy consumption. The net effect on systolic BP was –1 (95% CI –3, +1) mm Hg, and on diastolic BP –1, (–2, +0) mm Hg. No association was found between baseline BP,

soy protein or isoflavone dose and effect on BP. No significant effect of soy products was found for several markers of inflammation, vascular function, or lipid oxidation. Although the effect of soy products on menopausal symptoms are inconsistent across studies, the evidence of a benefit was stronger from the randomized trials of soy isoflavone supplements, but not of other soy products among post-menopausal women. This effect was not seen in the few studies among peri-menopausal women or those treated for breast cancer. Soy products do not appear to affect menstrual cycle length or estradiol level in pre-menopausal women, thyroid stimulating hormone, bone markers, or glucose metabolism. Small numbers of studies or inconsistency among studies precluded drawing conclusions regarding the effect of soy protein on other endocrine markers and other evaluated outcomes. For all outcomes, no soy protein or isoflavone dose-effect response or soy product type difference in effect was apparent across studies. The few studies that directly compared soy doses (generally isoflavone doses) for the most part also found no difference in effect based on dose. In general, soy products were well-tolerated, although study withdrawal due to aversion was more common in soy treatment arms than control arms. The most common adverse events reported were gastrointestinal or menstrual complaints although they were few in number.

Conclusions. A wide variety of soy products and formulations have been investigated for a large number of conditions. However, a large proportion of the studies suffer from poor reporting or study design, limiting conclusions. Soy products appear to exert a small benefit on LDL and triglycerides; these effects may be of small clinical effect in individuals, although possibly large enough to have a population-wide effect. The inconsistent association between soy protein dose and effect, and the lack of association between soy isoflavone dose and effect, limit possible determination of an appropriate amount of soy product needed for lipid reduction. Soy products may reduce menopausal symptoms in post-menopausal women. The current literature does not support other effects of soy products. However, other than menopausal- and menstrual-related symptoms, no clinical outcomes were evaluated. The evidence from human studies does not suggest any worrisome adverse events beyond mild gastrointestinal intolerance. Conclusions were often limited due to small numbers of studies or heterogeneity across studies.

Given the large amount of heterogeneity and inadequate reporting, particularly related to soy protein and isoflavone dose, many questions remain as to whether specific soy products in adequate doses may be of benefit in specific populations. Further, well-conducted studies are needed to clarify the effect of soy dose on lipid parameters and to determine whether soy components other than protein or isoflavones may be responsible for the lipid effects seen.

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Appendixes are available electronically at
http://www.ahrq.gov/downloads/pub/evidence/pdf/soyeffects/soy.pdf

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Effects of Soy on Health Outcomes

Summary

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Introduction

The aims of this evidence report are to summarize the current evidence on the health effects of soy and its isoflavones on the following: cardiovascular diseases, menopausal symptoms, endocrine function, cancer, bone health, reproductive health, kidney diseases, cognitive function, and glucose metabolism. In addition, safety issues and drug interactions of using soy and its isoflavones, as reported in the literature, are summarized. This report also summarizes the formulations of soy products and/or soy food used in clinical trials. The report was requested and funded by the National Center for Complementary and Alternative Medicine (NCCAM) and the Office of Dietary Supplements at the National Institutes of Health (NIH) and was conducted through the Evidence-based Practice Center (EPC) program at the Agency for Healthcare Research and Quality (AHRQ).

There is increasing interest in soy and health since the U.S. Food and Drug Administration approved a health claim in October 1999 for use on food labels stating that a daily diet containing 25 grams of soy protein, also low in saturated fat and cholesterol, may reduce the risk of heart disease. This claim was based on the beneficial results in reducing plasma low-density lipoprotein (LDL) levels from dozens of human controlled clinical trials.[1] The health claim, however, covers only soy protein, since research results surrounding soy isoflavones were controversial.[2] This report summarizes the current evidence on the health effects of soy and its isoflavones.

Methods

Key Questions

Five general questions are addressed in this report:

1. In the clinical trial literature, what formulations of soy were used? At what dose? For what purpose(s) (e.g., trial endpoints)?
2. Does current clinical trial evidence indicate that whole soy products and individual constituents of soy have an effect on:
   a. Cardiovascular events, risk factors, and measures;
   b. Menopausal symptoms;
   c. Endocrine function;
   d. Cancer and tumor-related biomarkers;
   e. Osteoporosis and osteoporosis risk factors;
   f. Reproductive health;
   g. Kidney function; and
   h. Other outcomes, based on results of Key Question 1, above?
3. What is the scientific evidence of a dose-response effect of different forms of soy and

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individual constituents of soy for the conditions specified in Key Question 1?

4. What are the frequency and type(s) of adverse events associated with consumption of soy that are reported in the scientific literature (both trials and epidemiology)?
5. What is the scientific evidence of a dose-response effect of whole soy products and individual soy constituents on their safety?

Approach to Analyzing the Literature

Inclusion Criteria

This report encompasses several health conditions and many outcomes of interest. Therefore, specific inclusion criteria were needed for each of the health conditions and sometimes for different outcomes of the same health condition. The common inclusion criteria for studies analyzed in this report consist of: human subjects 13 years and older; prospective studies including randomized controlled trials, cohorts, crossover and non-randomized comparison studies; at least five subjects in the soy arm; any health condition; quantification of the amount of soy; and reported outcomes of interest. In general, the minimum duration for all serum marker, urine marker, and vascular outcome studies was 4 weeks (exceptions are noted below, under "Specific Inclusion Criteria for Health Conditions Examined").

For assessments of adverse events, we also included prospective observation studies and case-control studies, with no limitations on study size or duration, or quantification of soy product.

Health Conditions of Interest

In addition to the health conditions of interest listed under Key Question 3, the Technical Expert Panel (TEP) convened by the EPC suggested the category of neurocognitive outcomes. NCCAM was also interested in knowing about research that might have been done in other health conditions. Therefore, our literature search was conducted to broadly include soy studies for any health conditions. We screened all citations to identify health conditions not on the list agreed upon with the TEP. During our review process, we included the additional category of endocrine function.

Soy Products (and Controls) Considered

We accepted studies that used soy supplements and foods that quantified the amount of soy ingredients or products. We categorized various soy products and soy food into the following groups:

- Refined soy products
  - Isolated soy protein with isoflavones
  - Isolated soy protein without isoflavones
  - Textured soy protein
  - Soy-derived isoflavone
    - Genistein/genistin
    - Daidzein/daidzin
    - Glycitein/glycitin
- Soy/soya food products (ingested amount must be quantified)
  - Whole soy beans (edamame)
  - Soy flour
  - Soy drink (soy milk)
  - Tofu (bean curd)
  - Miso
  - Other processed soy bean products (tempeh, natto, okara, etc.)

For the purpose of this report, all study arms with a soy product of any type were considered to be soy interventions. Only study arms with a non-soy intervention were categorized as controls.

Specific Inclusion Criteria for Health Conditions Examined

In addition to the common inclusion criteria listed above, with input from TEP members we established the following additional criteria and specific outcomes for each of the specific health conditions.

Cardiovascular Outcomes: These included total cholesterol, LDL, high density lipoprotein (HDL), triglycerides, lipoprotein(a) [Lp(a)], blood pressure (BP), C-reactive protein (CRP), homocysteine, endothelial function, systemic arterial compliance, and oxidized LDL. We also sought studies of clinical cardiovascular outcomes (e.g., death, myocardial infarction, angina) but found none. The list of outcomes was determined in consultation with the TEP, based on expert opinion of the likelihood of an effect on the outcomes, clinical importance, and estimates of the numbers of studies likely to be available.

Because of the relatively large number of available studies reporting on lipids, triglycerides, and blood pressure, it was decided with the TEP to limit inclusion of these studies to randomized controlled trials with a minimum of 10 subjects consuming a soy product. For all cardiovascular outcomes, we required a minimum duration of 4 weeks.

Menopausal Symptoms: Studies evaluated peri-menopausal women, post-menopausal women, or women on breast cancer therapies with menopausal symptoms. A minimum duration of 4 weeks was required for studies of menopausal symptoms.

Endocrine Function: We included in our analyses the following endocrine markers: testosterone, follicle stimulating hormone (FSH), total estradiol and thyroid stimulating hormone (TSH). In addition, we evaluated menstrual cycle outcomes. The decisions for which outcomes to investigate were based on expert opinion of the likelihood of an effect on the outcomes, clinical importance, and estimates of the numbers of studies likely to be available. Studies that did not report numerical data on effect for these outcomes were not summarized; however, these studies were maintained in the database. For all endocrine outcomes, we required a minimum duration of 4 weeks (or one menstrual cycle).

Cancer and Tumor-Related Biomarkers: To evaluate whether soy may prevent cancer or reduce cancer risk factors, we included only studies that recruited subjects without a diagnosis of cancer. We limited our analyses to studies with tumor-related biomarkers or cancer risk factors as outcomes and to studies of clinical cancer outcomes (e.g., diagnosis of prostate cancer). We did not include studies that used soy products as "treatments" for cancer. The only outcome that fulfilled these criteria was testosterone. The studies that reported testosterone as an outcome in men without diagnoses of cancer were analyzed in the endocrine section. The decision to investigate only testosterone was based on expert opinion of the likelihood of an effect on the outcomes and of its clinical importance. For all tumor-related biomarkers, we broadened the eligibility criteria to include a minimum duration of 1 week.

Bone Endpoints: For bone resorption and/or formation biomarkers, the general inclusion criteria were used, including a minimum duration of 4 weeks. Because effects on bone mineral density occur slowly over time, we used minimum study duration of 1 year, although we did briefly review studies with a duration less than 1 year.

Miscellaneous Outcomes: For all other outcomes (neurocognitive, kidney, glucose metabolism), the general inclusion criteria were used in combination with the restriction to populations without the related specific diseases or conditions.

Literature Search Strategy

We conducted a comprehensive literature search to address the key questions.* Primary literature searches for English language publications on soy studies were conducted in EMBASE on March 25, 2004; in MEDLINE® on April 20, 2004; and in CAB Abstracts on June 24, 2004. Search terms included subject headings and textwords with filters to limit the publications to English language and primary studies of the adult and adolescent human populations. Subject headings and textwords were selected so that the same set could be applied to each of the different databases. A supplemental search was performed in MEDLINE on April 30, 2004, to retrieve articles using the textword "miso." A search update was performed in MEDLINE In-Process & Other Non-Indexed Citations and MEDLINE on September 30, 2004, and in CAB Abstracts on October 4, 2004. A search of the TOXLINE® database was conducted in March 31, 2005, to identify additional reports of adverse events in humans. Additional sources of published and unpublished data were sought by contacting members of the TEP and from reference lists of selected review articles and meta-analyses.

Reporting of Evidence

Methodological Quality Grade

We used a three-category grading system (A, B, C) to denote the methodological quality of each study. This system defines a generic grading system that is applicable to varying study designs, including randomized controlled trials, cohort, and case-control studies:

A: Least bias; results are valid; a study that mostly adheres to the commonly held concepts of high quality.

B: Susceptible to some bias but not sufficient to invalidate the results; a study that does not meet all the criteria in category A.

C: Significant bias that may invalidate the results; a study with serious errors in design, analysis, or reporting.

Applicability Grade

In this report, the focus is on the U.S. population and on specific subgroups within that population (i.e., post-menopausal women, peri-menopausal women, pre-menopausal women, men, and people with relevant medical histories such as breast cancer). Even though a study may focus on a specific

* Appendix A (Search Strategy) is available electronically at www.ahrq.gov/clinic/tp/soytp.htm.

target population, limited study size, eligibility criteria, and the patient recruitment process may result in a narrow population sample that is of limited applicability, even to the target population. To address this issue, we categorized studies within a target population into one of three levels of applicability, which are defined as follows: sample is representative of the target population; sample is representative of a relevant subgroup of the target population but not the entire population; sample is representative of a narrow subgroup of subjects only and is of limited applicability to other subgroups.

Meta-analysis

Meta-analysis was performed for several cardiovascular outcomes. We used the random effects model for continuous outcomes to combine studies. We also performed several random effects model meta-regression analyses to explore possible reasons for discrepancies across studies and to address Key Questions related to dose-response.

Results

Soy Products

Soy supplements were used in about three-quarters of all the trials analyzed in this report; soy foods were used in the remaining trials. In this report, soy milk was categorized as a soy supplement. Among the soy supplement trials, 57 percent used soy protein with isoflavones, 36 percent used isoflavones alone, and 6 percent used soy protein without isoflavones. In about one-half of the soy foods trials, textured soy protein was used. Soy flour was used in about one-quarter of the soy foods trials. There are 146 separate treatment arms of soy supplementations and 68 separate treatment arms of soy foods or diets. Across studies, the total isoflavones ranged from 0 mg to 185 mg per day, and the total protein intake from soy ranged from 0 g to 154 g per day. It is notable that the median soy product dose across studies (36 g soy protein per day) was equivalent to over a pound of tofu daily or about 3 soy protein shakes daily.

Cardiovascular Endpoints

No study evaluated clinical cardiovascular events. A total of 68 randomized studies reported data on total cholesterol, LDL, HDL, and/or triglycerides. The total isoflavones ranged from 0 mg to 185 mg per day, with a median of 80 mg. Among studies with soy protein, the total protein intake from soy ranged from 14 to 113 g per day, with a median of 36 g. There is a great deal of heterogeneity in the effects found on lipoprotein and triglyceride levels. Overall, the majority of studies reported small to moderate effects on the lipids, despite a wide range of net effects for total cholesterol, LDL, and triglycerides. Sixty-one studies reported data on the effect of consumption of soy products on total cholesterol levels. The median net change compared to control was approximately –5 (interquartile range –10, +1) mg/dL decrease (about –2.5 percent). A meta-analysis of 52 studies that reported data on the effect of soy consumption on LDL levels yielded a statistically significant net decrease of 5 (95-percent confidence interval [CI] –8 to –3) mg/dL (about –3 percent). A meta-analysis of 56 studies that reported data on the effect of soy consumption on HDL levels found a statistically nonsignificant net change of +0.6 (95-percent CI –0.5, +1.8) mg/dL. A meta-analysis combining 54 studies that reported data on the effect of soy consumption on triglyceride levels yielded a net change of –8 (95-percent CI –11, –5) mg/dL (about –6 percent). Across studies, there is the possible suggestion that higher doses of soy protein are associated with greater LDL reduction among those with elevated baseline LDL (although not if studies with minimal soy protein doses are excluded) but not with HDL or triglycerides. Dose of isoflavones was not associated with effect for any lipid. Higher baseline LDL or triglycerides may also be associated with net effect for these two lipids; the effect of baseline HDL is unclear. For all lipids, in individual studies the effect of dose and baseline was generally inconsistent.

A total of 22 studies reported data on the effect of consumption of soy products on systolic and diastolic BP. Overall, across studies, there was no discernible effect.

Some of the well-known emerging risk factors for cardiovascular disease included for analysis in this report are: Lp(a), CRP, homocysteine, endothelial function, systemic arterial compliance, and oxidized LDL. The total numbers of studies that reported data on the effect of soy consumption are: 18 studies on Lp(a), 3 on CRP, 5 on homocysteine, 10 on endothelial function, 3 on systemic arterial compliance, and 13 on oxidized LDL. Across these studies, there is no discernible effect based on the type of soy products. The majority of studies were of poor quality with a narrow range of applicability. Given the limited evidence and poor quality of studies, no conclusions could be drawn on the beneficial or harmful effects of consumption of soy protein on these putative risk factors for cardiovascular disease.

Menopausal Symptoms

A total of 21 trials examined the effects of soy and/or its isoflavones on hot flashes and night sweats in women. These

trials generally measured frequency and severity of the symptoms. However, the investigators used a large number of vasomotor symptom scores or indexes that employed a variety of frequency intervals. These factors made meta-analyses unsuitable and limited the comparisons of results across studies. Furthermore, many of the studies had high withdrawal or dropout rates, which were frequently uneven between soy treatment and control arms, further limiting the validity of these trials. Overall, the effects of soy protein and/or its isoflavones are inconsistent across studies. Every trial found a decrease in hot flash frequencies or scores in both the treatment groups and the control groups. Thus, the results are difficult to interpret. A third of the studies found no or worsening effects compared to control; two-thirds showed that soy protein and/or its isoflavones either nonsignificantly or significantly decreased hot flash frequencies or scores compared to control in post-menopausal women. The evidence of a benefit was stronger among the randomized trials of isoflavone supplements, which mostly showed positive results—the net reduction in weekly hot flash frequency ranged from 7 percent to 40 percent. However, these trials are mostly rated as poor quality due to high dropout rates. Only four studies evaluated the effect of soy consumption on menopausal symptoms in peri-menopausal women or those receiving breast cancer therapy. Among these studies there is no evidence that soy consumption is better than control to reduce menopausal symptoms.

Endocrine Function

Measures of endocrine function from 50 trials were reported in 47 articles. Five studies with a total of 179 participants reported testosterone levels in healthy males before and after soy consumption. Four of these trials found a statistically nonsignificant decrease in testosterone levels. The small total number of subjects, as well as the low quality of these studies, precluded any meaningful conclusion. No statistically significant effect was found on FSH level, which is commonly measured in the initial evaluation of male and female infertility; results were conflicting.

Twelve studies reported estradiol levels at the follicular phase in 434 pre-menopausal women. The overall effect of soy on estradiol levels was not consistent. Most of the studies showed a trend for soy to reduce estradiol, although they failed to demonstrate a statistically significant effect. Six randomized trials reported the effect of soy on TSH. No overall effect of soy on TSH and thyroid function is clear.

An additional 11 trials (in 10 publications) evaluated the effect of soy on menstrual cycle length in pre-menopausal women. A wide range of soy interventions were used in these trials, making a conclusion on the effects from soy difficult. These trials did not show statistically significant changes in menstrual cycle length after treatments of soy and/or its isoflavones.

Cancer and Tumor-Related Biomarkers

Twenty-four trials evaluated subjects without a history of cancer for effects of soy on tumor-related biomarkers. No study reported the development of cancer as an outcome. Most studies measured the effect of soy on estrogens and estrogen metabolites as well as on estrogenicity indicators. There were also trials that evaluated correlations between soy and possible cellular pathways of cancer prevention. No causal relationship could be established between these markers and cancer because they do not represent known risk factors for cancer disease. Only four studies reported on testosterone level, which is a risk factor for prostate cancer and is discussed above under "Endocrine Function."

Bone Endpoints

Overall, 31 studies evaluated various markers of bone health, including bone mineral density (BMD), bone formation biomarkers (bone specific alkaline phosphatase and osteocalcin) and bone resorption biomarkers (urinary hydroxyproline, urinary cross-linked N-telopeptide, urinary pyridinoline, and urinary deoxypyridinoline).

Because there are few long-term randomized trials and a wide variety of soy interventions used across studies, it is difficult to draw an overall conclusion about the effects of soy on bone outcomes. Overall, among the five studies of 1-year minimum duration, no consistent effect on BMD was seen with soy consumption. Studies of shorter duration likewise found no effect of soy. Similar to the results for BMD, studies of bone formation biomarkers generally found no effect of soy consumption when compared to control. While a number of studies reported reductions in two markers of bone resorption—urinary pyridinoline and deoxypyridinoline—no effects were found on the other markers of bone resorption, and the effects were not consistent across studies. For these markers, there is no clear evidence of a dose effect for either soy isoflavones or soy protein.

Only one study found a consistent effect on these markers. The study differed from other studies in that it evaluated a unique formulation of soy genistein and that it excluded subjects with denser femoral neck BMD.

Kidney Function, Neurocognitive Function, and Glucose Metabolism

Only one small study in patients with type 2 diabetes assessed the effect of soy on kidney function. No statistically significant change in glomerular filtration rate was seen after 8 weeks of soy protein diet. Four studies examined the effects of soy on cognitive function of post-menopausal women and college students of both sexes. Overall, no statistically significant or consistent effect was noted on neurocognitive functions such as verbal episodic memory. Six studies evaluated the effect of soy on fasting blood glucose. No statistically significant changes were reported.

Adverse Events

In general, the rates of adverse events reported were greater in the soy treatment arms than in their respective control arms, but adverse events related to soy consumption were generally minor. Overall, soy products including isoflavones were well tolerated in the trials we examined.

The most frequently reported adverse events among a total of 3,518 subjects in 49 studies (including 5 nonrandomized and 3 pharmacokinetic studies) that reported adverse events were gastrointestinal in nature. These were reported in 33 of 41 comparison studies of soy diets, soy proteins, isoflavones, and phytoestrogen supplements. Most of the gastrointestinal adverse events were reported in soy diet and soy protein trials, especially the 12 studies that used purified isoflavone interventions in dosages ranging from 40 to 100 mg/day. The amount of soy protein in these trials ranged from 20 to 60 g/day, but there was no clear dose relationship between the amount consumed and subsequent adverse events. Menstrual complaints, reported in 15 studies, were also common. Six of these studies used purified isoflavone interventions in dosages ranging from 40 to 80 mg/day. However, most women in these studies were post-menopausal, and the controls frequently included hormone therapy regimens. Other adverse events included musculoskeletal complaints, headache, dizziness, and rashes. In addition, there were somewhat more withdrawals from the soy arms due to taste aversion.

Limitations

Despite the large number of trials that have been performed, the health effects of soy for many conditions that have been studied remain uncertain. The methodological quality of over half the studies (about 55 percent) evaluated in this report was poor (Grade C). One-third of the poor-quality studies were either uncontrolled single-cohort studies, nonrandomized comparative studies, or comparative studies for which it was unclear whether they were randomized. Another third of the poor-quality studies had dropout rates that exceeded 20 percent or unequal dropout rates between the soy and control arms. Other reasons that studies were graded poor quality included lack of reporting of baseline data; inadequate accounting of important confounders; major discrepancies between text, tables, and/or figures or irreconcilable data that indicate likely improper statistical analysis; and substantial missing data.

There was also great heterogeneity among studies, particularly among the interventions analyzed. Comparisons across the myriad types of soy are intrinsically very difficult. This difficulty was compounded by the use of soy both as a supplement and as an integral part of the diet; furthermore, for numerous studies, it is difficult to distinguish between supplement and diet. It is likely that studies of supplements and diet are not easily comparable. Most studies involved a small number of study subjects and were of short duration. About one-half of studies were of less than 12 weeks duration and about one-third were shorter than 6 weeks. Few studies directly compared soy products, mostly comparing soy protein with varying amounts of soy isoflavones. Only one performed a factorial design study comparing both present and absent soy protein and present and absent soy isoflavones, thus allowing analysis of the effect of both soy protein and soy product. The universal issue of possible publication bias, where negative studies are less likely to be published and are more likely to be published later, is a potential concern. However, for most outcomes, the majority of studies reported negative outcomes, and there was no obvious evidence of publication bias among the lipid studies (where there is evidence of a positive effect).

Conclusions

Most of the studies evaluated the effects of soy on various biomarkers or measures, not clinical outcomes, although several of the endpoints, such as blood pressure, LDL, and bone mineral density, do have known meaningful correlations with clinical outcomes. Cardiovascular surrogate endpoints were assessed by the largest number of studies. Overall, soy was found to have a small effect on lipids. However, the duration of these studies was generally short, and it is uncertain whether the results would be sustained. No study evaluated clinical cardiovascular disease.

Reduction of hot flashes by soy was seen in trials involving post-menopausal and peri-menopausal women. Most of the trials lasted only 3 to 4 months; thus the long-term benefits remain unclear. In addition, different measurements were used to assess benefits across studies, making comparisons and synthesis difficult. Soy phytoestrogens are seen by some as an alternative to estrogen therapy to treat post-menopausal symptoms. However, the estrogenic effect of soy in potentially promoting tumor recurrence raises concern for its use by breast cancer survivors. The current literature provides no data to address this issue.

The evidence does not support an effect of soy products on endocrine function, menstrual cycle length, or bone health, although evidence was often limited and of poor quality. No study evaluated clinical endocrine or bone disease.

This report was limited to human studies, and thus was unable to fully respond to biological or biochemical hypotheses of benefits or harms of phytoestrogens suggested by various animal, in vitro, or assay detection studies: the correlations between specific nutrients and their effects remain unclear. While the evidence does suggest a greater likelihood of adverse events with soy consumption, these were mostly minor in nature. There were a limited number of studies with duration of 1 year or longer; thus the long-term adverse effect of soy in a large population is uncertain.

For all outcomes, including adverse events, there is no conclusive evidence of a dose-response effect for either soy protein or isoflavone. However, for LDL reduction, there is a suggestion of a possible dose-response effect for soy protein.

Future Research

This report dealt with a broad range of health conditions and endpoints; thus it is difficult to focus research recommendations on a specific area. As is the case with most bodies of evidence regarding medical fields, better quality, well-reported, larger, and longer duration studies are needed to address the questions of interest. Future studies should fully report the components of soy products being tested; compare different doses, soy products, and populations; more closely evaluate the effects of different soy components, including non-protein, non-isoflavone components; fully consider the types of foods being replaced by soy products and the controls being used; and use the CONSORT statement as a guide to designing and reporting studies.[3,4]

Conducting clinical trials in the area of health effects of food substances is fraught with difficulties. There is a complex interplay among the various components and potentially active substances within the foods and with other foods. Dietary variations, as well as other lifestyle and clinical variations among individuals, are also complex. Controlling for these factors is difficult within a trial. Interpreting discrepant results among trials is even more difficult. Isoflavones are believed to be the key active substance in soy, but this is by no means certain. Little data suggest that the amount of soy isoflavones is associated with an incremental effect, and studies of soy protein with little or no isoflavones frequently had similar effects as isoflavone studies. Difficulties with attempting to ascribe a food health benefit to a specific component of the food are highlighted by the recent spate of disappointing results from antioxidant trials, which suggest that the evaluation of potential nutrient benefits may need a paradigm different from the traditional clinical trial model.

The bioavailability of an ingested nutrient may also be an important factor in the determination of the beneficial effect. Several factors may affect the bioavailability of ingested nutrients: (1) absorption rate, which is affected by the interactions with competitive nutrients, the usual diet compositions, and types of foods or supplements; (2) incorporation rate into the blood stream, in which complex mechanisms might be involved, such as the functions of facilitated transporters, receptors on the membrane, or cellular binding proteins; (3) metabolism of the intestinal bacterial environment. Any one of these factors alone does not determine the bioavailability. In order to gain insights on the question of dose-response relationship, we need information not only on the soy isoflavone contents, including types and amount, but also on the bioavailability of the ingested soy isoflavones.

Unfortunately, studies that attempt to control for the myriad factors that interfere with clear interpretation of the effect of food products such as soy tend to be highly artificial, with little applicability to the average person. Clarity is needed to define what study questions are of interest. Metabolic laboratory studies or investigations of highly structured or restricted diets (such as those where soy protein constitutes the bulk of daily protein consumption) are of potential value only to possibly determine which components of soy are bioactive or to determine what extremes of diet may be necessary to achieve a benefit. Studies that substitute practical amounts of soy products into average people's diets would better address

the question of whether people should make the effort to include more soy in their diets, but these studies will invariably be difficult to interpret. An exception to this may be studies of soy isoflavone supplements (e.g., nonfood capsules), which may be interpreted more like usual drug trials.

Carefully controlled efficacy studies (those conducted under the artificial conditions of a clinical trial) may still be useful to pin down the relative effects of various components of soy. Once this is better clarified, more practical effectiveness studies that aim to test the value of an intervention in more real-world scenarios with feasible interventions might be more important.

Availability of the Full Report

The full evidence report from which this summary was taken was prepared for the Agency for Healthcare Research and Quality (AHRQ) by the Tufts-New England Medical Center Evidence-based Practice Center under Contract No. 290-02-0022. It is expected to be available in August 2005. At that time, printed copies may be obtained free of charge from the AHRQ Publications Clearinghouse by calling 800-358-9295. Requesters should ask for Evidence Report/Technology Assessment No. 126, *Effects of Soy on Health Outcomes.* In addition, Internet users will be able to access the report and this summary online through AHRQ's Web site at www.ahrq.gov.

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Evidence Report

Chapter 1. Introduction

This evidence report has been prepared by the Tufts-New England Medical Center (Tufts-NEMC) Evidence-based Practice Center (EPC) concerning the effect of soy consumption on various diseases and conditions, including but not restricted to cardiovascular, kidney and gastrointestinal diseases, cancer, osteoporosis, menopausal symptoms, and reproductive health. This report was requested and funded by the National Center for Complementary and Alternative Medicine (NCCAM) and the Office of Dietary Supplements of the National Institutes of Health (NIH), through the EPC program at the Agency for Healthcare Research and Quality (AHRQ).

There is increasing interest in soy and health since the U.S. Food and Drug Administration (FDA) approved a health claim in October 1999 for use on food labels stating that a daily diet containing 25 grams of soy protein, also low in saturated fat and cholesterol, may reduce the risk of heart disease. This claim was based on the beneficial results in reducing plasma low-density lipoprotein (LDL) levels from dozens of human controlled clinical trials.[1] The health claim, however, covers only soy protein, since research results surrounding soy isoflavones were controversial.[2] The aims of this report are to summarize the formulations of soy products and/or soy food used in clinical trials, and to reflect the current evidence on the health effects of soy and its isoflavones on the following: cardiovascular disease (CVD), menopausal symptoms, endocrine function, cancer, bone health, reproductive health, kidney disease, cognitive function, and glucose metabolism. In addition, safety issues and drug interactions of using soy and its isoflavones as reported in the literature are summarized.

Metabolism and Mechanisms of Actions of Soy and Its Isoflavones

Soy is a legume commonly consumed by many Asians, although most Americans do not regularly eat it. Despite the increase in the consumption of soy products since the approval of the soy health claim in 1999, only a small number of Americans who believe that soy consumption is "healthy" consume soy products at least once a week, according to a survey by the United Soybean Board.[2] Soybean and soy foods, such as tofu, tempeh, soy drinks, soy flours, and meat alternatives or analogs, are rich in soy protein and soy isoflavones. The isoflavones are among the phenolic compounds produced by soy, and a class of phytoestrogens, or plant-derived estrogens. Soy sauce and soybean oil are soy-derived foods, but lack substantial amounts of either soy protein or soy isoflavones.[3]

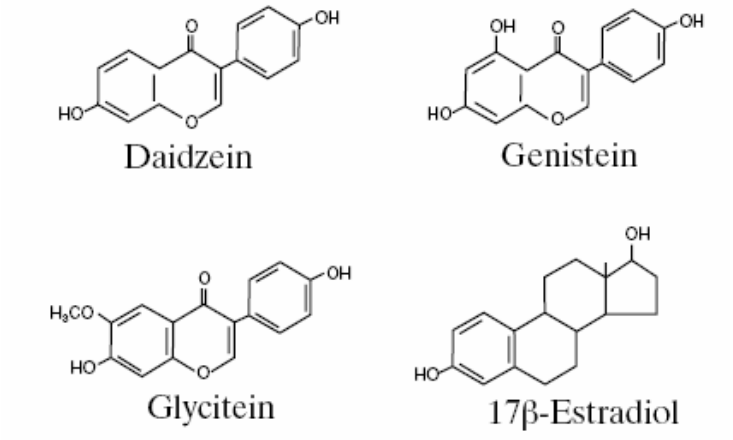

Figure 1 Chemical structures of genistein, diadzein, glycitein and estradiol

Soy isoflavones are one of

the families of phytoestrogens that are similar in chemical structure to estrogen and thus may have similar effects (Figure 1). The most prominent isoflavones in soy are daidzein, genistein, glycitein, and their glucosides. Most isoflavones occur in plants in the bound form of their glucosides, daidzin, genistin and glycitin, and are biologically inactive. The glucoside forms of isoflavones can be converted to free forms (aglycones) after consumption by hydrolysis at the intestinal brush border membrane and by intestinal bacteria. The efficiency of this conversion affects bioavailability, and subsequent metabolism. Different food sources of soy isoflavones can also affect their bioavailibilities. One aglycone, equol, (7-hydroxy-3-(4'-hydroxyphenyl)-chroman), is an exclusive intestinal bacterial metabolite of dietary isoflavones.[4,5] Equol has superior antioxidant potencies against destructive compounds, known as free radicals[1], than the parent isoflavones.[6] However, many adults do not produce equol. This phenomenon has led to the terminology of being an "equol-producer" or "non-equol producer" and may explain the differential clinical effectiveness among individuals of isoflavones from soy proteins.[7] There are many other factors that might influence the health effects of soy and its isoflavones, such as the relevant window of exposure (early in life, peri-menopausal or post-menopausal) or the frequency of exposure.

The aglycone form of soy isoflavones and their metabolites can be absorbed by the gut and may exert several biological effects. There is a growing interest in the roles of these natural estrogenic or antioxidant substances in influencing disease progression or medical conditions in humans. Research suggests several mechanisms of action of soy isoflavones.

Isoflavones as Estrogens and Anti-Estrogens

Estrogens produced in the ovaries and testes stimulate growth, blood flow, and water retention in the sexual organs and are also associated with the development of breast and endometrial cancers.[8] Because of the structural similarity of soy isoflavones to estrogens, it has been suggested that these isoflavones might act as either an agonist or antagonist of estrogen. For example, studies suggest that genistein can induce responses similar to estradiol in breast, ovarian, endometrial, prostate, vascular and bone tissues, and in cell lines.[9-12] Genistein can also act as an estrogen antagonist in some tissues. Animal studies have shown that genistein inhibits the development of chemically-induced mammary cancer.[13,14]

Isoflavones as Cancer-Enzyme Inhibitors

Genistein was first identified in 1987 as an inhibitor of protein-tyrosine kinase, an enzyme that promotes cancer cell growth.[15] Other cancer-related enzymes were also found to be inhibited by genistein, including DNA topoisomerases I and II[16] and ribosomal S6 kinase.[17] Possible mechanisms for the anti-proliferative properties of genistein include prevention of cell mutations by stabilization of cell DNA and reduction of cell oxidants, reduction in capacity of malignant cells to metastasize by inhibiting angiogenesis and subsequent tumor growth, as well as inducing cell differentiation.[18]

[1] Free radicals are highly reactive substances that result from normal metabolism and from exposure to environmental factors like cigarette smoke and ultraviolet light. They cause cellular damage by attacking the body's cell membranes, proteins, and DNA.

Isoflavones as Antioxidants

Isoflavones' antioxidant properties may enhance the resistance of LDL to oxidation and prevent free radical damage to DNA.[19] Studies show that genistein has greater antioxidant activities than other isoflavones.[6,17] Genistein may also increase the production of antioxidant enzymes, such as superoxide dismutase.[20]

New concepts are still evolving about possible mechanisms of action of soy isoflavones. For example, some research suggests the potential health effects of soy isoflavones might occur via the transforming growth factor β signaling pathway.[21]

Possible Roles of Soy and its Isoflavones in Influencing Diseases or Conditions in Humans

Although direct evidence is lacking, it has been suggested that soy and its isoflavones affect various diseases or conditions, such as CVD, cancers, osteoporosis, menopausal symptoms, and kidney disease, through different mechanisms of action described above.

Cardiovascular Disease and its Risk Factors

Heart disease is, in part, a hormone-dependent disease, as illustrated by the lower age-related incidence in pre-menopausal women compared with males and a rise in incidence among both natural and surgical post-menopausal women.[18] Although estrogen replacement therapy does not reduce long-term CVD risk in post-menopausal women,[22] soy isoflavones may reduce CVD risk by several mechanisms. One possible pathway for the protective effects of soy isoflavones on CVD may be manifested through blood lipid changes.[1] There has also been a suggestion that soy isoflavones may have regulatory effects on blood pressure (BP).[23]

Menopausal Symptoms

The reported incidence of hot flashes varies among menopausal women in different countries. For example, it occurs in 70 to 80 percent of menopausal women in Europe, 57 percent in Malaysia, and 18 and 14 percent in China and Singapore, respectively. The estrogenic effects of soy isoflavones may be responsible for modifying the incidence rates, given that substantial dietary differences in soy consumption exist among these populations.[18] Soy isoflavones may regulate menopausal symptoms by maintaining normal vascular function in both vasomotor tone and vessel wall compliance.[24,25] However, it is not clear which components of soy may be responsible for any putative effects.

Cancers and Their Risk Factors

Several observational studies have evaluated the effects of isoflavones on the risk of developing hormone-dependent cancers, such as breast, colon, prostate, endometrial, and ovarian. Much of the evidence is based on the differences in the consumption of soy products in different areas of the world.[18] Case-control studies examining the association between soy-containing food intake and breast cancer risk suggest a marginally significant inverse relationship.[26,27] However, no significant association between soy-based foods and breast cancer risk was found in a large prospective cohort study in Japan or other prospective studies.[26]

A recent meta-analysis of stomach cancer studies conducted among Asians showed that non-fermented soy foods significantly reduced the risk of stomach cancer while fermented soy

foods had no effect.[28] But because various confounders such as dietary salt, fruit, and vegetable intake, were not adjusted for in the original studies, the role of soy could not be adequately assessed. A case-control study and the preliminary finding from an ongoing clinical trial suggest an inverse relationship between soy-based food and colon cancer risk.[25,29]

Bone Health - Osteoporosis and Fracture Risk

The pathophysiological mechanism for involuntary bone loss in post-menopausal women can be explained by the deficiency of estrogen due to a rapid decline in ovarian function. It involves loss of both cancellous and cortical bone and continues throughout the remainder of life. It is caused by the loss of estrogen effects on extra-skeletal calcium homeostasis, leading to decreased intestinal calcium absorption, increased renal calcium wasting, and, perhaps also effects on vitamin D metabolism and loss of a direct effect on the parathyroid gland that decreases parathyroid hormone (PTH) secretion.[30] These factors put post-menopausal women at an increased risk of developing osteoporosis and fracture.

Conventional therapies for treating osteoporosis in women, such as estrogen treatment alone or combination estrogen and progesterone, function as inhibitors of bone resorption. However, the effectiveness and safety of hormone replacement therapies in post-menopausal women remain controversial. The potential use of soy and its isoflavones to preserve bone tissue and delay or prevent the onset of osteoporosis has recently been addressed.[9] Benefits from soy protein for bone health may also be related to changes in dietary protein intake, and calcium excretion. Since the animal protein-rich diet is associated with the highest excretion of undissociated uric acid and calcium, it increases the risk of kidney stones and osteoporosis.[31] Substituting less hypercalciuric soy protein for animal protein may benefit calcium balance and bone health.

Kidney Disease

Low protein diets can halt or attenuate the progression of chronic kidney disease, and modifications in the quality of dietary protein can also affect the course of kidney disease. In animal models of kidney disease, studies have shown that soy protein diets limit or reduce proteinuria and kidney lesions associated with progressive kidney failure.[32] However, it is not clear whether the kidney protective effects of soy protein diets are due to soy isoflavones or other soy components. The effect of soy protein intake on kidney function in humans has not been examined comprehensively. In a review of studies of people with different types of chronic kidney disease, soy protein moderated proteinuria and preserved kidney function, although most of the trials reviewed were of relatively short duration and involved small numbers of patients.[32] The applicability of these findings to prevent the development of chronic kidney disease in people with normal kidney function is uncertain.

Reproductive Health

Reproductive health is defined by the World Health Organization (WHO) as a state of physical, mental, and social well-being in all matters relating to the reproductive system at all stages of life. This definition of reproductive health implies that people are able to have a satisfying and safe sex life and that they have the capability to reproduce and the freedom to decide if, when, and how often to do so (http://www.who.int/topics/reproductive_health/en). While reproductive health covers a wide range of issues including contraception safety and efficacy, fertility, infertility, and HIV/AIDS and other sexually transmitted diseases the focus of

this report is on fertility. The putative estrogenic effect of soy may have a direct impact on endocrine function, which in turn may affect fertility.

Other Diseases or Conditions

Studies have also reported on the use of soy-based foods combined with hypocaloric diet in the treatment of obesity, but no significant effect of soy was found when compared to the control treatment.[33,34] Soy-rich foods have also been used to prevent malnutrition in patients with Crohn's disease, a chronic inflammatory disorder of the bowel. A study reported that patients with inactive Crohn's disease had a higher treatment compliance while on a soy-rich and lactose-free diet than on a conventional enteral diet, although body weight and lean muscle mass were increased equally in both groups of patients.[35] A population-based cohort study in China showed an inverse relationship between intake of soy products and the risk of glycosuria in post-menopausal women, but not in pre-menopausal women.[36] Estrogen loss associated with menopause may contribute to the development of Alzheimer's Disease.[37] However, a cohort study of Japanese-American men reported that higher midlife consumption of soy in the form of tofu was associated with indicators of cognitive impairment and brain atrophy in late life.[38]

Although soy has been evaluated for treatment or prevention of a variety of diseases, this report – which evaluates the effect of soy on generally healthy people and not on disease treatment – evaluates only a limited number of other conditions, based primarily on the availability of data. These include endocrine function, cognitive function, and glucose metabolism.

Chapter 2. Methods

Overview

This evidence report on the health effects of soy is based on a systematic review of the literature. The Tufts-New England Medical Center Evidence-based Practice Center (Tufts-NEMC EPC) held meetings and teleconferences with a technical expert panel (TEP) to identify specific issues central to this report. The TEP was comprised of technical experts in soy research and in relevant health areas of interest. A comprehensive search of the medical literature was conducted to identify studies addressing the key questions. Evidence tables of study characteristics and results were compiled, and the methodological quality and the applicability of studies were appraised. Study results were summarized with both qualitative and quantitative reviews of the evidence, summary tables, and meta-analyses, as appropriate.

A number of individuals and groups supported the Tufts-NEMC EPC in preparing this report. The TEP served as our science partner. It included technical experts, representatives from the Agency for Healthcare Research and Quality (AHRQ) and from the National Center for Complementary and Alternative Medicine (NCCAM) and the Office of Dietary Supplements at the National Institutes of Health (NIH). The TEP worked with the EPC staff to refine key questions, identify important issues, and define parameters for the report. Additional clinical domain expertise was obtained through local experts who joined the EPC. A draft version of this report was critically appraised by a panel of peer reviewers.[*] Revisions were made based on their comments; although all statements within the report are those of the authors only.

Key Questions Addressed in this Report

1. In the clinical trial literature, what formulations of soy were used? At what dose? For what purpose(s) (e.g., trial endpoints)? (Section 3.1)

2. Does current clinical trial evidence indicate that whole soy products and individual constituents of soy have an effect on (Sections 3.2-3.8):
    a. cardiovascular events, risk factors, and measures;
    b. menopausal symptoms;
    c. endocrine function;
    d. cancer and tumor-related biomarkers;
    e. osteoporosis and osteoporosis risk factors;
    f. reproductive health;
    g. kidney function; and
    h. other outcomes, based on results of Key Question 1 above?

3. What is the scientific evidence of a dose-response effect of different forms of soy and individual constituents of soy for the conditions specified in Key Question 1? (Section 3.9)

[*] Appendix D (Peer Reviewers) is available electronically at www.ahrq.gov/clinic/tp/soytp.htm.

4. What are the frequency and type(s) of adverse events associated with consumption of soy that are reported in the scientific literature (both trials and epidemiology)? (Section 3.10)

5. What is the scientific evidence of a dose-response effect of whole soy products and individual soy constituents on their safety? (Section 3.10)

Approach to Analyzing the Literature

The key questions in this report sought to discover the breadth and depth of soy research that has been conducted in humans to assess its effect on various health outcomes. This information will be used by NCCAM and the Office of Dietary Supplements to help identify research opportunities in soy. As the focus of the report is not to elaborate the effect of soy on a specific health condition, a single causal pathway or analytic framework is not appropriate for this report. Figure 1 in Chapter 1 illustrates the diverse potential mechanisms of soy on various health conditions.

To guide the assessment and synthesis of the literature, we used an expanded version of the generally-referred-to "PICO" method (Participants, Intervention, Comparator, Outcomes) to define the parameters of interest. With input from the TEP, we asked the following questions to establish the literature review criteria:

- What are the populations of interest?
- What are the interventions of interest?
- What are the comparators of interest?
- What are the (marker/intermediate and clinical) outcomes of interest?
- What are the health conditions of interest?
- What are acceptable study designs?

Inclusion Criteria

This report encompasses several health conditions and many outcomes of interest. Therefore, specific inclusion criteria were needed for each of the health conditions and sometimes for different outcomes of the same health condition. In this section, we first describe the common inclusion criteria for any study included in this report, regardless of the health condition evaluated. This is followed by additional specific criteria for each of the health conditions.

The common inclusion criteria for studies analyzed in this report consist of: human subjects 13 years and older; prospective studies including randomized controlled trials, cohorts (including prospective epidemiological studies), cross-over and non-randomized comparison studies; at least 5 subjects in the soy arm; any health condition; quantification of the amount of soy; and reported outcomes of interest. In general, the minimum duration for all serum marker, urine marker, and vascular outcome studies was 4 weeks (exceptions are noted below, under *Specific Inclusion Criteria for Health Conditions Examined*).

For assessments of adverse events, we also included prospective observation studies and case-control studies, with no limitations on study size or duration, or quantification of soy product.

Health Conditions of Interest

In addition to the health conditions of interest listed under Key Question 3, the TEP suggested the category of neurocognitive outcomes. NCCAM and the Office of Dietary

Supplements were also interested in knowing about research that might have been done in other health conditions. Therefore, our literature search was conducted to broadly include soy studies for any health conditions. We screened all citations to identify health conditions not on the list agreed upon with the TEP.

During our review process, we created the category of endocrine outcomes, which incorporates many of the reproductive hormones and potential cancer risk factor studies.

Soy Products (and Controls) Considered in this Report

We accepted studies that used soy supplements and foods that quantified the amount of soy ingredients or products. We categorized various soy products and soy foods into the following groups:

- Refined soy products
    - Isolated soy protein with isoflavones
    - Isolated soy protein without isoflavones
    - Textured soy protein
    - Soy derived isoflavone
        - genistein/genistin
        - daidzein/daidzin
        - glycitein/glycitin
- Soy/soya food products (ingested amount must be quantified)
    - Whole soy beans (edamame)
    - Soy flour
    - Soy drink (soy milk)
    - Tofu (bean curd)
    - Miso
    - Other processed soy bean products (tempeh, natto, okara, etc.)

We also categorized studies based on whether the soy products were consumed in the form of a supplement or as part of the overall diet. In general, we relied on the studies' descriptions of the products and their use to make this determination. The categorization of soy milk, however, was problematic as approximately equal numbers of studies described its consumption as either a dietary replacement of other beverages or as a supplement to be added to subjects' regular diet; many studies reported insufficient details to determine how the soy milk was being used. In consultation with the TEP, we (arbitrarily) categorized all soy milk studies as supplement studies, in order to standardize our evaluation. Where necessary, sensitivity analyses were done regarding this categorization.

For the purpose of this report, all study arms with a soy product of any type were considered to be soy interventions. Only study arms with a non-soy intervention were categorized as controls. This is in contrast to many studies that considered soy protein without isoflavones to be the control. Since we were interested in the effect of both soy protein and soy isoflavones, we categorized these study arms as soy interventions.

Specific Inclusion Criteria for Health Conditions Examined

In addition to the above common inclusion criteria, with input from TEP members we established the following additional criteria and specific outcomes for each of the specific health conditions.

Cardiovascular outcomes

We included in our analyses cardiovascular outcomes listed in 5 in Chapter 3. We also sought studies of clinical cardiovascular outcomes (e.g., death, myocardial infarction, angina) but found none. The list of outcomes was determined in consultation with the TEP. The decisions for which outcomes to investigate were based on expert opinion of the likelihood of an effect on the outcomes, clinical importance, and estimates of the numbers of studies likely to be available.

Because of the relatively large number of available studies reporting on lipids, triglycerides, and blood pressure, it was decided with the TEP to limit inclusion of these studies to randomized controlled trials with a minimum of 10 subjects consuming a soy product. For all cardiovascular outcomes, we required a minimum duration of 4 weeks.

Menopausal Symptoms

We evaluated studies of peri-menopausal and post-menopausal women for menopausal symptoms. A minimum duration of 4 weeks was required for studies of menopausal symptoms.

Endocrine Function

We included in our analyses the following endocrine outcomes: testosterone, follicle stimulating hormone (FSH), total estradiol and thyroid stimulating hormone (TSH). Because menstrual cycle length is directly related to female reproductive hormones, this outcome is included in this section. The decisions for which outcomes to investigate were based on expert opinion of the likelihood of an effect on the outcomes, clinical importance, and estimates of the numbers of studies likely to be available. Studies that did not report numerical data on effect for these outcomes were not summarized; however, these studies were maintained in the database. For all endocrine outcomes, we required a minimum duration of 4 weeks.

Cancer and Tumor-Related Biomarkers

To evaluate whether soy may prevent cancer or reduce cancer risk factors, we included only studies that recruited subjects without a diagnosis of cancer. We did not include studies that used soy products as "treatments" for cancer. We limited our analyses to studies with tumor-related biomarkers or cancer risk factors as outcomes and to studies of clinical cancer outcomes (e.g., diagnosis of prostate cancer). The only outcome that fulfilled these criteria was testosterone. The studies that reported testosterone as an outcome in men without diagnoses of cancer were analyzed in the endocrine section. The decision to investigate only testosterone was based on expert opinion of the likelihood of an effect on the outcomes, and clinical importance. For all tumor-related biomarkers, we broadened the eligibility criteria to include a minimum duration of 1 week.

Bone outcomes

For bone resorption and/or formation biomarkers, general inclusion criteria were used, including a minimum duration of 4 weeks. Because effects on bone mineral density occur slowly over time, we used minimum study duration of 1 year; although we did briefly review studies of less than 12 months.

Miscellaneous outcomes

For all other outcomes (neurocognitive, kidney, glucose metabolism), the general inclusion criteria were used in combination with the restriction to populations without the related specific diseases or conditions. Thus, studies of cognitive function outcomes were restricted to populations without Alzheimer's disease, dementia, or mental retardation at baseline. Studies of

kidney function outcomes were restricted to those populations without kidney disease at baseline. Studies of glucose metabolism were restricted to populations without diabetes.

Reproductive health

Based on the included studies in our systematic review, outcomes that could address reproductive health issues in men and women are hormones related to fertility status as well as menstrual cycle length in women, which is used in the initial assessment for female infertility. The goal of the initial infertility evaluation of the couple is to determine the likely cause of the infertility and to determine the most logical approach to treatment. The initial evaluation for male factor infertility should include a reproductive history and two properly performed semen analyses. An initial endocrine evaluation should include at least a serum testosterone and FSH. Endocrine evaluation should be performed if there is: (1) an abnormally low sperm concentration, especially if less than 10 million/mL; (2) impaired sexual function; or (3) other clinical findings suggestive of a specific endocrinopathy. The initial evaluation for female factor infertility should include a reproductive history and documentation of ovulation, which is usually done with over the counter ovulation kits. An initial endocrine evaluation includes day three FSH level and estradiol.

Exclusion Criteria

We excluded studies that investigated soy products that were mixed with other potentially active ingredients (e.g., soy and fish oil) where the effect of the soy could not be separated from the other ingredients. Studies that compared combinations to similar products without soy (e.g., soy + estrogen vs. estrogen) were included. We also excluded soy products that are used as an ingredient of enteral feedings. In addition, we excluded the following studies:

- Review articles (no primary data)
- Non-trial observational studies
- Animal or in vitro studies
- Age less than 13 years
- Not English language
- Fewer than 5 subjects in the soy arm of the trial (unless adverse event reported)
- Ingested soy amount not quantified
- Not soy, soy protein, soy isoflavone
- Insignificant amount of total daily protein or isoflavones in the soy product (e.g., soy sauce, soy oil; case by case determination was made in collaboration with technical experts)
- Mixed soy product or nutrition/diet drink (e.g., brands such as Boost, Ensure, GeniSoy, Met-Rx, Revival Soy, Slim Fast) where other active ingredients may be present
- Studies that report serum or urine levels of isoflavones or amino acids achieved instead of amount ingested
- Study of serum or urine isoflavone levels without data on clinical outcomes or risk factors
- Studies that evaluated only soy allergies
- No outcome of interest

Literature Search Strategy

We conducted a comprehensive literature search to address the key questions.[*] Primary literature searches for English language publications on soy studies were conducted in EMBASE on March 25, 2004, in MEDLINE on April 20, 2004, and in CAB Abstracts on June 24, 2004. Search terms included subject headings and textwords with filters to limit the publications to English language and primary studies of the adult and adolescent human populations. Subject headings and text words were selected so that the same set could be applied to each of the different databases. A supplemental search was performed in MEDLINE on April 30, 2004 to retrieve articles using the textword "miso". A search update was performed in MEDLINE In-Process & Other Non-Indexed Citations and MEDLINE on September 30, 2004, and CAB Abstracts on October 4, 2004. A search of the TOXLINE database was conducted in March 31, 2005 to identify additional reports for adverse events in humans. Additional studies were sought by contacting members of the TEP, and from reference lists of selected review articles and meta-analyses.

Study Selection and Data Extraction

All citations identified through the literature search were screened according to the inclusion criteria. A low threshold for acceptance was used at this stage to maximize the retrieval of potentially useful studies. Retrieved articles were evaluated against the complete inclusion criteria.

A single reviewer extracted each eligible study.[†] Data extraction problems were addressed during weekly meetings. Occasional sections were re-extracted to ensure that uniform definitions were applied across extracted studies. Problems and corrections were noted through spot checks of extracted data and during the creation of summary and evidence tables. A second reviewer independently verified the data in the summary tables using the original article. Items extracted included: factors related to study design (randomization method, allocation concealment method, blinding, study duration, and funding source), population characteristics (country, eligibility criteria, demographics, co-morbid conditions, concomitant medications, and baseline diet), interventions and comparison groups (description of soy product and control interventions or diets, including amount of specific protein), outcomes of interest (number enrolled and analyzed, intermediate and clinical outcomes, adverse events, reasons for withdrawals, results [including baseline value, final value, within-treatment change or between-treatment difference, and variance, as reported]), and whether each study addressed each of the key questions. In addition, each study was categorized based on applicability and study quality as described below.

Grading of the Evidence

Studies accepted in evidence reports have been designed, conducted, analyzed, and reported with varying degrees of methodological rigor and completeness. Deficiencies in any of

[*] Appendix A (Search Strategies) is available electronically at www.ahrq.gov/clinic/tp/soytp.htm.
[†] Appendix B (Data Extraction Form) is available electronically at www.ahrq.gov/clinic/tp/soytp.htm.

these components can lead to biased reporting and interpretation of the results. While it is desirable to grade individual studies to highlight the degree of potential bias, the grading of study quality is a challenging process. Most factors commonly used in quality assessment of randomized controlled trials do not demonstrate a consistent relationship to estimates of treatment effects.[39] Thus, there is still no uniform approach to grade studies. Our EPC has adopted the following approach in our previous evidence reports.

Methodological Quality Grade

We used a 3-category grading system (A, B, C) to denote the methodological quality of each study. This grading system has been used in most of the previous evidence reports from the Tufts-NEMC EPC as well as in evidence-based clinical practice guidelines.[40] This system defines a generic grading system that is applicable to varying study designs including randomized controlled trials, cohort, and case-control studies:

A Category A studies have the least bias and results are considered valid. A study that adheres mostly to the commonly held concepts of high quality including the following: a formal randomized study; clear description of the population, setting, interventions and comparison groups; sufficient power (arbitrarily defined as minimum sample size of 30 subjects); clear description of the content of the intervention used (including both amount of soy protein and amount of soy isoflavones); appropriate comparator (with similar amount and distribution of fats); appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; double-blinding; no reporting errors; less than 20% dropout; clear reporting of dropouts; and no obvious bias.

B Category B studies are susceptible to some bias, but not sufficient to invalidate the results. They do not meet all the criteria in category A because they have some deficiencies, but none likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems.

C Category C studies have significant bias that may invalidate the results. These studies have serious errors in design, analysis or reporting, have large amounts of missing information, or discrepancies in reporting. Specific criteria included large (>20%) or unequal dropout rate, large discrepancy in baseline and final numbers of subjects, non-randomized or single-cohort studies, dissimilar baseline values among cohorts, unclear duration or numbers of subjects, missing baseline data, or irreconcilable apparent differences between data in figures, tables, and text.

Where different quality criteria applied to different outcomes within a study (e.g., missing baseline data for a specific outcome), quality grades may differ for different outcomes within the same study. In addition to applying these 3 grading systems, additional comments relating to potential sources of bias and other study limitations were recorded by each investigator during the data extraction process. Such comments are included in the evidence tables.

Methodological quality scoring was performed near the end of the review when we had the most experience and knowledge about the included studies. Each included study was graded by at least 2 people (with the exception of studies with major deficiencies, such as a non-comparative study design). When there were disagreements, 1 or 2 additional reviewers graded

the studies and consensus was reached. Approximately half the studies had quality scoring by 3 or more reviewers.

Applicability Grade

Applicability addresses the relevance of a given study to a population of interest. Every study applies certain eligibility criteria when selecting study subjects. Most of these criteria are explicitly stated (e.g., disease status, age, sex). Some may be implicit or due to unintentional biases, such as those related to study country, location (e.g., community vs. specialty clinic), or factors resulting in study withdrawals. The question of whether a study is applicable to a population of interest (such as Americans) is distinct from the question of the study's methodological quality. For example, due to differences in the background diets, an excellent study of Japanese men may be very applicable to people in Japan, but less applicable to Japanese American men, and even less applicable to African American men. The applicability of a study is thus dictated by the questions and populations that are of interest to those analyzing the studies.

In this report, the focus is on the US population and on specific subgroups within that population (i.e., post-menopausal women, peri-menopausal women, pre-menopausal women, men, and people with relevant medical histories, such as breast cancer). Even though a study may focus on a specific target population, limited study size, eligibility criteria, and the patient recruitment process may result in a narrow population sample that is of limited applicability, even to the target population. To address this issue, we categorized studies within a target population into 1 of 3 levels of applicability that are defined as follows:

Sample is representative of the target population. It should be sufficiently large to cover both sexes (as appropriate for a given outcome), a wide age range, and other important features of the target population (e.g., background diet).

Sample is representative of a relevant sub-group of the target population, but not the entire population. Limitations include such factors as narrow age range, single ethnicity, narrow range of risk for relevant diseases (e.g., hyperlipidemia).

Sample is representative of a narrow subgroup of subjects only, and is of limited applicability to other subgroups. For example, a study of the oldest-old men or a study of a population on a highly controlled diet.

Reporting Results

Results of Comparative Studies

Most of the outcomes of interest were continuous variables such as blood pressure and lipid levels. For these outcomes, the summary tables describe 3 sets of data: the mean baseline level in the soy arm, the net change of the outcome, and the reported *P* values of the difference between the soy and the control arms. The net change of the outcome is the difference between the change in the soy arm and the change in the control arm:

$$\text{Net change} = (\text{Soy}_{\text{Final}} - \text{Soy}_{\text{Initial}}) - (\text{Control}_{\text{Final}} - \text{Control}_{\text{Initial}}).$$

While some studies reported adjusted and unadjusted within-arm and between-arm (net) differences, to maintain consistency across studies, we calculated the unadjusted net change

using the above formula for all studies when the data were available. All exceptions and caveats are described in footnotes to the summary tables.

We included only reported *P* values for the net differences. We did not calculate any *P* values, but, when necessary, used provided information on the 95% confidence interval or standard error (SE) of the net difference to determine whether it was less than 0.05. We included any reported *P* value less than 0.10. Those above 0.10 and those reported as "non-significant" were described as "NS" (non-significant) in the tables.

For measures expressed using standard or Systeme International (SI) units (e.g. lipid levels), the original units reported in the study were included in the evidence tables. However, all such measurements were converted to standard units in the summary and results tables to facilitate comparisons.

Meta-Analysis

Meta-analysis was performed for several cardiovascular outcomes. We used the random effects model for continuous outcomes to combine studies. Studies were included only if they reported sufficient data to estimate both mean net change (or mean within-cohort change for specific sub-analyses) and SE of the net change (or of the within-cohort change).

The random effects model assigns a weight to each study that is based both on the individual study variance and the between-study heterogeneity. Compared with the fixed effect model, the random effects model is more conservative in that it results in broader confidence intervals when between-study heterogeneity is present.

For the meta-analyses, we required data on both the mean change in outcome level and the SE of the change. However, many studies provided only the SEs for the baseline and final outcome levels. In order to include these studies in analysis we had to make several assumptions to estimate the SE of the change. To do this we used the equation:

$$SE_{12} = \sqrt{(SE_1^2 + SE_2^2 - 2 \times \rho \times SE_1 \times SE_2)}$$

where SE_1, SE_2, and SE_{12} are the SEs for baseline, final and change, respectively, and ρ is the correlation between SE_1 and SE_2.[41] We arbitrarily chose the correlation, ρ, to be 0.50, the mid-point value. In our experience, using different values for ρ generally results in similar estimates of SE.

For each soy cohort, the SE of the net change was then calculated using the standard calculation for determining the SE of 2 independent cohorts. Namely the above equation where the correlation factor $\rho = 0$ and thus the final term drops out. Where studies reported either within-cohort SEs or net change SEs, these numbers were used.

An important caveat in our analyses is that for studies with multiple soy cohorts but single non-soy cohorts, we assumed that the estimated net changes (and their SEs) are independent of each other despite their shared control groups. In addition, we made a number of "corrections" to the reported data where there were apparent errors (such as reporting standard deviation as SE or reporting mean values and SEs in different units [e.g., mg/dL and mmol/L]). Where within-cohort or net changes were reported graphically, we preferentially used tabulated data for baseline and final values; although we estimated values and SEs from graphs when necessary. Net changes reported as percentage changes were ignored when baseline values from the soy and non-soy cohorts were not identical.

Meta-analyses were performed for all eligible studies of low density lipoprotein (LDL), high density lipoprotein (HDL), triglycerides, and blood pressure. These outcomes were chosen for meta-analysis based on potential clinical relevance and the number of available studies.

Subgroup and Meta-Regression Analyses

To explore potential reasons for differences of results across studies and to evaluate possible dose-effects, we performed several meta-regressions analyses with the continuous variables soy protein dose, soy isoflavone dose, and mean baseline outcome value. We used a random-effects regression model as described by Berkey et al. [42] This model adjusts each study's weight in the regression by the degree of heterogeneity across all included covariates. Both multivariate and univariate analyses were performed. When appropriate, sub-analyses were performed to explain factors related to the meta-regressions.

In addition, we performed sub-group meta-analyses based on the following sub-groups, when appropriate:

- Study treatment arms with normal versus abnormal mean baseline outcome values (e.g., LDL less than and greater than 130 mg/dL)
- Study treatment arms with different types of soy products:
    - Protein with isoflavone
    - Protein with isoflavone (without soy milk)
    - Soy milk
    - Protein without isoflavone
    - Isoflavone alone
- Study treatment arms where soy was consumed as dietary replacement and as a supplement
- Study quality A or B versus quality C
- Outlier studies omitted.

In order to complement a previously published meta-analysis,[43] we also performed a meta-analysis of

- High versus low dose soy isoflavones treatment arms among studies that investigated multiple isoflavone doses
    - All high-dose cohorts versus lowest dose
    - Only highest-dose cohort versus lowest dose

For all outcomes, when there were sufficient studies, we examined all these same factors, in addition to study population and sex (when relevant) to determine if there was evidence of a differential effect based on these factors. We also specifically evaluated studies that either performed direct comparisons between treatments or reported sub-group analyses. In consultation with the TEP, it was decided to not evaluate equol-production status of study subjects. This decision was made based on the current lack of applicability of any findings of differences between equol producers and non-producers, since no one outside soy studies knows their equol production status.

Evidence and Summary Tables

The evidence table offers a detailed description of the studies that addressed each of the key questions. The evidence table is available via the internet.* The table provides information about the study design, patient characteristics, inclusion and exclusion criteria, interventions evaluated, and comparison groups evaluated. Each study appears once regardless of how many

* Appendix C (Evidence Table) is available electronically at www.ahrq.gov/clinic/tp/soytp.htm.

interventions or outcomes were reported. Studies are ordered alphabetically by the first author, then by publication date, then by MEDLINE unique identifier number.

Summary tables are included in each Results section. They succinctly report summary measures of the main outcomes evaluated. They include information regarding study duration, study size (of subjects analyzed), intervention and control, outcome measures, study population, and methodological quality, and study applicability. These tables were developed by condensing information from the evidence tables. They are designed to facilitate comparisons and synthesis across studies. Studies reporting multiple outcomes may appear several times in summary tables.

Description of the soy interventions includes quantification of the amount of aglycone isoflavones and the amount of soy protein, when available. When studies did not specify whether measured isoflavones were aglycones or glucosides, or when studies reported only glucoside amounts, this is indicated in the footnotes. Outcome units and metrics are reported in standard units and as in common metrics, regardless of how these were reported in the articles. These tables include baseline values of relevant outcomes, within-cohort changes (Final – Baseline) in these values, reported *P* values of the within-cohort changes, net changes compared to control (as defined above, under *Results of Comparative Studies*), and reported *P* values of the net changes. In addition, reported *P* values of differences in effect between different soy treatment arms are included. Within-cohort and net changes were calculated from reported data when necessary (these values are italicized). Blank cells indicate that the relevant data were not reported in the articles.

Studies are categorized and ordered as follows. Diet studies are above supplement studies; randomized cross-over studies are above randomized parallel controlled trials, which are above non-controlled or other non-randomized studies; studies that used dairy controls are above animal protein or usual diet controls, which are above miscellaneous controls, which are above studies with no non-soy control. Within each of these categories, studies are ordered from largest to smallest number of subjects consuming soy products.

Adverse Events Reporting

We used the term adverse event as defined by the World Health Organization (WHO) International Conference on Harmonization. An adverse event is "any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product." An adverse drug reaction is any "noxious and unintended response to a medicinal product related to any dose…" (www.fda.gov/cder/guidance/iche2a). For the purpose of this report, soy or soy ingredient is substituted for pharmaceutical product. We reviewed all accepted and rejected human studies in the analyses of soy effects for data on adverse events and drug interactions. These reports included randomized trials, cohorts, case-control studies, and individual case reports and series. We excluded articles that reported "bad taste", "aftertaste", or "lack of palatability" as adverse events as well as those that reported negative conclusions such as "there were no immunological effects" or "there was no increase in pancreatic size". While adverse events attributable to soy in animal studies and changes in biomarkers in in-vitro studies might be indicative of potential toxicities in humans and would be useful in the overall evaluation of safety issues, the review of this body of literature is beyond the scope of this report.

We summarized adverse events in several tables. Adverse events were grouped according to the study design and the type of soy product used. In these tables we report for each study the data on the number of subjects, trial duration, interventions and controls, and the adverse events. Based on the adverse event data we compiled, we grouped them into menstrual-related and gastrointestinal-related complaints, withdrawals due to any effects, and a miscellaneous category. A separate table was created for studies that stated that no adverse events occurred.

Chapter 3. Results

Searches in EMBASE and MEDLINE yielded 2,639 and 2,650 citations, respectively, with an additional 10 citations from the supplemental search. After removal of overlapping and duplicate publications, the final yield was 4,471 citations. An updated search conducted in early December yielded an additional 308 citations.

After screening of the titles and abstracts, 599 articles were retrieved for examination. A total of 178 clinical trials publications were included in sections of the report regarding soy effects. In addition to these studies, 5 prospective cohorts and 3 pharmacokinetics studies reported data on adverse events. The results are summarized in this chapter in the following order: soy products used in the trials (Section 3.1), effects of soy on cardiovascular endpoints (3.2) , menopausal symptoms (3.3), endocrine endpoints (3.4), cancer and tumor related biomarkers (3.5), bone endpoints (3.6), reproductive health (3.7), and a miscellaneous category that includes kidney, neurocognitive, and glucose metabolism endpoints (3.8). Following is an overview of association of dose and product type with effect (3.9). Finally, adverse events from clinical trials and observational studies are summarized following the review of evidence on health outcomes (3.10).

All qualifying studies are presented in summary tables in the appropriate sections. Details regarding these studies are available in the evidence table.[*] Some additional studies that contained pertinent information, but did not qualify for inclusion are also discussed.

3.1. Soy Products Used

(Tables 1-4)

Key Question 1: In the clinical trial literature, what formulations of soy were used? At what dose? For what purpose(s) (e.g., trial endpoints)?

Table 1 summarizes soy supplements or soy protein powders and beverages. Table 2 summarizes soy foods or diets used in the experimental arms of the studies by each outcome category. Many of the soy protein products derive from the same manufacturer presumably, due to merger and acquisition. Specific study endpoints and the formulations of soy supplements and soy foods are described in both evidence tables* and summary tables later in this chapter. Studies in the category of "unclear amount of soy protein and/or isoflavones" did not quantify the amount of soy interventions used.

A total of 281 comparisons were made with soy supplements or with soy foods/diets in the experimental arms. About three-quarters of these were trials of soy supplements, as isoflavones alone, soy protein with or without isoflavones. About one-half of the trials of soy supplements or soy foods and diets focused on one or more of the many cardiovascular endpoints. About 20% of the trials studied endocrine function. About 10-15% each, of the trials, evaluated menopausal symptoms or menstrual cycle length, bone outcomes, or cancer markers/risk factors. Less than 5% of the trials evaluated neurocognitive function, kidney function, or glucose metabolism. Over

[*] Appendix C (Evidence Table) is available electronically at www.ahrq.gov/clinic/tp/soytp.htm.

90% of the soy supplement trials used isoflavones alone or soy protein with isoflavones; there were more trials of soy protein with isoflavones than trials of isoflavones alone.

Across studies, the total isoflavones ranged from 0 mg to 185 mg per day and the total protein intake from soy ranged from 0 g to 154 g per day. Of note, the median soy product dose across studies (36 g soy protein per day) was equivalent to over a pound of tofu daily or about 3 soy protein shakes daily.

The isoflavone content of evaluated soy products is presented in Tables 3 and 4.

Table 1. Soy supplements or soy protein powders and beverages used in the experimental arm of the studies

Outcome Categories	Isoflavones Alone	Soy Protein with Isoflavones	Soy Protein without Isoflavones	Unclear Amount of Soy Protein and/or Isoflavones	Total # of Studies*
Cardiovascular	Total: 23 Advanced Care Products (1) Bonette (Novomed, Helsinki) (2) Eugenbio (1) Genistein, Lab Plant (2) NovaSoy (ADM) (3) Novogen (1) PhytoLife (1) Protoveg (2) Soya hypocotyl Iso (Fuji Oil Co) (2) Soycreme (1) Total Life Co (1) No brand name tablet (6)	Total: 60 Abacor (2) Abalon (Nutri Pharma, Oslo) (1) Altima HP-20 (Protein Technologies International) (2) [b] Calcimel (1) Eden (1) FXP HO 159 (1) ISP powder (not specific) (19) Proderma (ALPRO, Belgium) (2) Solae – powder (2) [b] Supro – powder (12) [b] Supro – liquid/beverage (6) Supro – tablet/cap (1) [b] Soymilk (8) Tofuline (1) Unilever Best Foods, Brazil (1)	Total: 7 Essential Nutrition (1) Protein Technologies International (6) [b]	Total: 4 ADM (1) ISP powder (not specific) (2) Scan Diet Shakes (1)	94
Menopausal Symptoms and Menstrual Cycle Length	Total: 12 Advanced Care (1) Bonette (Novomed, Helsinki) (1) Genistein, Lab Plant (1) PharmaVite (2) PHYTO SOYA (Glycine max. L. Merr.) (1) Phytosoya (1) Protoveg (2) Solgar Italia (1) Soylife™ (Netherlands) (1) SOYSELECT™ (1)	Total: 15 Banyang Foods (2) ISP powder (ADM) (1) ISP powder—Protein Technologies International (5) [b] ISP powder (not specified) (1) Kibun Food Chimifa (1) Soya World (1) Supro – powder (1) [b] Supro 675-powder (1) [b] TakeCare™ (PTI) (2) [b]			27
Endocrine	Total: 21 Advanced Care Products (1) Bonette (Novomed, Helsinki) (1) Eugenbio (1) Genistein, Lab Plant (4) Genistein-combined polysaccharide (GCP, Amino Up Chem Co) (1) NovaSoy (ADM) (4) PharmaVite (1) Regen soy extract (Novogen Ltd) (1) SOYSELECT™ (1) Total Life Co (1) No brand name tablet (5)	Total: 17 ADM Euro-port (1) Banyang Foods (1) ISP powder (not specific) (2) Kibun Food Chemifa, Tokyo (3) Soymilk (2) Supro – powder (6) [b] TakeCare™ (PTI) (2) [b]	Total: 1 Essential Nutrition (1)		39

continued

Table 1. Continued

Outcome Categories	Isoflavones Alone	Soy Protein with Isoflavones	Soy Protein without Isoflavones	Unclear Amount of Soy Protein and/or Isoflavones	Total # of Studies*
Tumor related	Total: 7 NovaSoy (ADM) (2) PharmaVite (1) Protoveg (1) SOYSELECT™ (1) Total Life Co (1) No brand name tablet (1)	Total: 9 Banyang Foods (2) Protein Technologies International- powder (5) [b] Soymilk (1) Supro – powder (1) [b]			16
Bone	Total: 7 Advanced Care Products (1) Bonette (Novomed, Helsinki) (1) Genistein, Lab Plant (1) NovaSoy (ADM) (1) Total Life Co (1) Isoflavone extracts (No brand) (2)	Total: 12 ISP powder—Protein Technologies International (7) [b] ISP powder—Solae (1) [b] Proderma, ALPRO Belgium (1) SoGood Soymilk drinks (1) Supro 675 (2) [b]	*Total: 4* ISP powder—Protein Technologies International (4) [b]		23
All other outcomes	Total: 3 Healthy Woman soy menopause supplement (1) PHYTO SOYA (Glycine max. L. merr.) (1) Solgen (Solbar Plant Extracts) (1)	Total: 5 DuPont Protein Technologies—powder (1) [b] Fortimel (1) Soy beverage (1) Supro – powder (2)			8
Total # of Studies [a]	74	118	12	4	207

[a] The numbers do not add up to the total due to single study may examine multiple outcome categories
[b] In October 1997 Ralson Purina completed its sale of Protein Technologies International (PTI) to DuPont. Solae is the trademark for PTI.

Table 2. Soy foods or diets used in the experimental arm of the studies

Outcome Categories	Tofu Alone	Soybean Alone	Soy Flour or Foods Made from Soy Flour	Other Soy Food	Texture Soy protein or Soy Diet (Mixed Soy Foods)	Total N of Studies*
Cardiovascular	Total: 4 Blue Lotus Foods (2) Mori-nu Silken Extra Firm tofu (1) Tofu (1)	Total: 2 Soybean diet (2)	Total: 5 Nutrisoy flour (ADM Europort) (2) Soy crisp bread (1) Soy flour (1) Soy flour (Soy Products of Australia) (1)	Total: 3 Isosoy Soy germ (1) Nijiru (1) SoGood Soy nuts (1)	Total: 22 Texture Soy protein - Cholsoy L (3) Texture Soy protein (1) Soy protein and/or Isoflavone Unclear (18)	36
Menopausal Symptoms and Menstrual Cycle Lengths			Total: 3 Nutlettes® --soy flour and corn cereal (1) Soy flour (1) Soy-grits bread (George Weston Foods) (1)		Total: 2 Soy protein and/or Isoflavone Unclear (2)	5
Endocrine	Total: 3 Blue Lotus Foods (2) Tofu (1)	Total: 1 Soybean product (1)	Total: 3 ADM Euro-port (1) Soy flour (2)	Total: 2 Isosoy Soy germ (1) Soy nuts (1)	Total: 4 Soy protein and/or Isoflavone Unclear (4)	13
Cancer			Total: 3 Nutrisoy flour (ADM Europort) (1) Soy Bread (1) Soy flour (1)		Total: 2 Soy protein and/or Isoflavone Unclear (2)	5
Bone		Total: 1 Soybean diet (1)	Total: 2 Soy flour (1) Soy-grits bread (George Weston Foods) (1)	Total: 4 Natto (1) Nijiru (1) Roasted hypocotyl germ of soybean & sesame(1) Soy nuts (1)	Total: 1 Soy protein and/or Isoflavone Unclear (1)	8
All other outcomes		Total: 1 Soya Bean (1)	Total: 1 Soy Flour, Rakosvolgye Co (1)	Total: 1 Almased (1)	Total: 4 Soy protein and/or Isoflavone Unclear (4)	7
Total # of Studies [a]	7	5	17	10	35	74

[a] The numbers do not add up to the totals due to studies examining multiple outcome categories.
w/ = with; w/o= without; SP and/or Isoflavone Unclear = Unclear Amount of Soy Protein and/or Isoflavones

Table 3. Isoflavone content of soy products with isolated soy protein and isoflavones

	Daily Dose of Isoflavones (mg/ day) per gram of Soy Protein			
	Genistein	**Daidzein**	**Glycitein**	**Total Isoflavones**
Abacor ISP (PTI)	--	--	--	3.70
Abacor yogurt (PTI)	--	--	--	1.85
Abalon (Nutri Pharma, Oslo, Norway)	--	--	--	>3.3
Calcimel	4.44	3.50	--	7.94
Essential Nutrition ISP(Brough, UK)	2.33	1.63	0.43	4.40
FXP HO 159 (PTI)	--	--	--	3.70
ISP96 powder (PTI)	1.30	0.70	--	2.40
ISP90 powder (PTI)	0.98	0.65	0.18	1.80
ISP80 powder (PTI)	1.20	0.60	0.20	2.00
ISP56 powder (PTI)	0.65	0.35	0.10	1.08
ISP38 powder (PTI)	1.74	1.16	0.26	3.16
Protoveg, Direct Foods (Manchester UK)	0.33	0.42	--	0.75
Solae ISP powder	2.00	1.58	0.23	≥3.81
Soymilk (Kibun Food Chimica,Tokyo, Japan)	--	--	--	6.42
Soymilk (Proderma/ALPRO, Belgium)	1.00	1.12	0.97	3.08
Soymilk (Unilever Best Foods, Brazil)	2.00	1.32	0.20	3.48
Soymilk (Banyang Foods, Houston, TX)	2.25	1.82	--	4.06
Supro powder high in isoflavones	1.32	0.89	0.19	2.42
Supro powder low in isoflavones	0.66	0.45	0.09	1.21
TakeCare™ (PTI)	1.40	0.71	0.09	2.20

Individual isoflavone doses may not add up to total due to rounding errors and presence of other isoflavones.
ISP = isolated soy protein, PTI = Protein Technology Institute, Inc.

Table 4. Isoflavone content of soy products with isoflavones only

	mg/day			
	Genistein	**Daidzein**	**Glycitein**	**Total Isoflavones**
Acatris high-dose isoflavones (Netherlands)	12	38	31	80
Acatris low-dose isoflavones (Netherlands)	6	19	16	40
Bonette (Novomed, Helsinki, Finland)	6	42	66	114
Eugenbio (Seoul, South Korea)	70	19	11	100
Genistein, Lab Plant (Messina, Italy)	54	0	0	54
Healthy Woman soy menopause supplement	--	--	--	110
Novasoy (ADM)	44	44	2	90
PharmaVite (San Fernando, CA)	--	--	--	76
Regen soy extract (Novogen, N.Ryde, Australia)	--	--	--	40
Solgar Italia (Padua, Italy)	11	36	25	76
Solgen (Solbar Plant Extracts, Ashdod, Israel)	--	--	--	60
Soya hypocotyls isoflavones (Fuji Oil Co, Japan)	2	17	10	40
Soylife soy extract (Netherlands)	12	40	28	80
Total Life Co (Taipei, Taiwan)	--	--	--	150

Individual isoflavone doses may not add up to total due to rounding errors and presence of other isoflavones.

Key Question 2: *Does current clinical trial evidence indicate that whole soy products and individual constituents of soy have an effect on:*

a. cardiovascular events, risk factors, and measures (Section 3.2);
b. menopausal symptoms (Section 3.3);
c. endocrine function (Section 3.4);
d. cancer and tumor-related biomarkers (Section 3.5);
e. osteoporosis and osteoporosis risk factors (Section 3.6);
f. reproductive health (Section 3.7);
g. kidney function (Section 3.8.1); and
h. other outcomes, based on results of Key Question 1 above (Sections 3.8.2-4)?

3.2. Cardiovascular Events, Risk Factors, and Measures

3.2.1. Summary of Studies Found

(Tables 5-6)

A very large number of cardiovascular risk factors and measures have been investigated in the medical literature. In consultation with the Technical Expert Panel (TEP), we have focused our review to those outcomes that have either been commonly examined in studies of soy consumption or are of particular interest in relation to soy consumption. We also tracked the number studies that have investigated a defined list of outcomes of secondary interest. Table 5 lists the outcomes included here and the other tracked outcomes, along with the number of studies found for each outcome. The numbers of non-analyzed, tracked studies are estimates only, as errors in tracking these outcomes were not systematically searched for.

The reviewed risk factors and measures are discussed in the following, largely arbitrary, order: lipids [total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), triglycerides, lipoprotein (a) [Lp(a)]], blood pressure, C-reactive protein (CRP), homocysteine, non-serum diagnostic tests (endothelial function and systemic arterial compliance), followed by oxidized LDL. All analyzed studies are shown in Table 6. Those studies indicated with the letter "t" reported qualitative data on the given outcomes (e.g., "no significant effect"), but did not report quantitative data.

We also searched for prospectively designed studies that investigated the effectiveness of soy consumption for reducing clinical cardiovascular disease or events. However, no such studies were found.

Studies of low-calorie diets designed to promote weight loss were excluded from analyses of cardiovascular risk factors and measures because of the strong effect such diets exert on all analyzed cardiovascular outcomes. None of the remaining studies reported substantial weight loss by study subjects; thus, we did not attempt to further exclude studies based on weight loss. Furthermore, because of the great number of studies that reported data on total cholesterol, LDL, HDL, and triglycerides, we employed stricter eligibility criteria for these outcomes. We analyzed only randomized trials that analyzed at least 10 subjects who consumed a soy product. Tables 5 and 6 reflect these eligibility criteria.

Table 5. Number of studies that reported on each cardiovascular outcome.

Analyzed Outcomes	Number of Studies [a]	Section	Other Outcomes	Number of Studies [b]
Total cholesterol [c]	66	3.2.2	Cardiovascular events or disease	0
Low density lipoprotein (LDL) [c]	56	3.2.3		
High density lipoprotein (HDL) [c]	62	3.2.4	Apolipoprotein A-1	24
Triglycerides [c]	58	3.2.5	Apolipoprotein B	27
Lipoprotein (a) [Lp(a)]	21	3.2.7	Apolipoprotein C-III	0
Blood pressure (BP)	25	3.2.8	Apolipoprotein E	2
C-reactive protein (CRP)	3	3.2.9	Endothelin	4
Homocysteine (Hcy)	5	3.2.10	E-selectin	3
Endothelial function	10	3.2.11	Factor VII	3
Systemic arterial compliance	3	3.2.12	Factor VIII	0
Oxidized LDL	13	3.2.13	Factor XII	0
Total	**83**		Fibrinogen	4
			Free or non-esterified fatty acids	1
			Intercellular adhesion molecule (ICAM)	2
			Interleukin 2R or 6	3
			Nitrous oxide (NO)	0
			P-selectin	1
			Remnant-like particles	0
			Thrombomodulin	0
			Vascular cell adhesion molecule (VCAM)	2
			von Willebrand Factor (vWF)	1
			Ankle-brachial index	0
			Bleeding time	0
			Carotid ultrasound/Doppler	0
			Coronary angiography	0
			Echocardiography	0
			Electrocardiogram (ECG) parameters	0
			Exercise tolerance testing (ETT)	0
			Heart rate variability	0
			Intima-media thickness (IMT)	0
			Platelet aggregation	1

[a] Studies reported in multiple articles are not double-counted.
[b] Estimates. Studies reported in multiple articles may be double-counted.
[c] Only randomized trials with a minimum of 10 subjects who consumed soy products.

Table 6. Summary of studies reporting cardiovascular outcomes.

Author Year (UI)	TC	LDL	HDL	Tg	Lp(a)	BP	CRP	Hcy	Endothelial Function	Systemic Arterial Compliance	Oxidized LDL
Ashton 2000 10694766		x									
Ashton 2000 11194529	x		x	x	x						x
Azadbakht 2003	x	x	x	x							
Bakhit 1994	x	x	x	x							
Baum 1998	x		x	x							
Blum 2003 12659466	x	x	x	x					x		
Bricarello 2004	x	x	x	x							x
Burke 2001						x					
Carroll 1978	x										
Chiechi 2002 11836040	x	x	x	x		x					
Crouse 1999	x	x	x	x	t						
Cuevas 2003	x	x	x	x		x			x		
D'Amico 1992						x					
Dent 2001	x	x	x	x	x						
Dewell 2002	x		x	x							
Gallagher 2004	x	x	x	x							
Gardner 2001	x	x	x	x							
Gardner-Thorpe 2003	x	x	x	x							x
Gentile 1993						x					
Goldberg 1982	x	x	x	x							
Gooderham 1996	t		t								
Han 2002	x	x	x	x		x					
Hermansen 2001	x	x	x	x	x	x		x			
Hill 2004											x
Jayagopal 2002	x	x	x	x		x					
Jenkins 1999	x	x	x	x	x	x					x
Jenkins 2000 10647066											x
Jenkins 2000 10778882											x
Jenkins 2002 12077742							x				
Jenkins 2002 12145008	x	x	x	x	x	x		x			x
Kanazawa 1995											x
Kreijkamp-Kaspers 2004	x	x	x	x	x						
Kreijkamp-Kaspers 2005						x			x		
Kurowska 1997	x	x	x	x		x					x
Lichtenstein 2002	x	x	x	x							
Lissin 2004	x	x							x		
Mackey 2000	x	x	x	x							
Meinertz 1988	x	x	x	x							
Meinertz 1989	x	x	x	x							
Meinertz 2002	x	x	x	x	t						
Merz-Demlow 2000	x	x	x	x	x						
Meyer 2004	x	x	x	x	x	x				x	
Murkies 1995	x		x	x							
Murray 2003	x	x	x	x							
Nestel 1997	x	x	x	x			x	x			x
Nikander 2003 14602747									x		
Nikander 2004 15240647	x	x	x	x	x	t					
Nilausen 1999					x						
Onning 1998	x	x	x	x							
Petri 2004	x	x	x	x							

Continued.

Table 6. Continued

Author Year (UI)	TC	LDL	HDL	Tg	Lp(a)	BP	Endothelial Function	Systemic Arterial Compliance	CRP	Hcy	Oxidized LDL
Potter 1993	x	x	x	x							
Puska 2002	x	x	x	x	x					x	
Puska 2004	x	x	x	x		x				x	
Rivas 2002						x					
Sagara 2004	x		x			x					
Scambia 2000	t	t	t	t							
Scheiber 2001											x
Shorey 1981	x		x	x							
Simons 2000	x	x	x	x	x	x	x				
Sirtori 1999	x	x	t	t		t					
Sirtori 2002	x	x									
Squadrito 2002	x	x	x	x		x					
Squadrito 2003							x				
Steinberg 2003	x	x	x	x			x				x
Swain 2002	x	x	x	x	x						
Takatsuka 2000	x	x	x	x							
Teede 2001	x	x	x	x	x	x	x	x			
Teede 2004									x		
Teixeira 2000	x		x	x	x						
Tonstad 2002	x	x	x	x	x					x	
Uesugi 2002	x	x	x	x							
Uesugi 2003	x		x	x							
Upmalis 2000	t	t	t	t							
Van Horn 2001	x	x	x								
Verrillo 1985	x	x	x	x							
Vigna 2000	x	x	x	x	x	x					
Wangen 2001	x	x	x	x	x						
Washburn 1999	x	x	x	x		x					
Watanabe 2000 11216491	t	t	t								
Wong 1995	x										
Wong 1998 Hyperlipidemia	x	x	x	x							
Wong 1998 Normolipidemia	x	x	x	x							
Yildirir 2001					x		x				

t = results reported in text only, no data reported
TC = total cholesterol; LDL = low density lipoprotein; HDL = high density lipoprotein; Tg = triglycerides; Lp(a) = lipoprotein (a); BP = blood pressure; CRP = C-reactive protein; Hcy = Homocysteine; UI = MEDLINE, EMBASE, or CAB Abstracts unique identifier.

3.2.2. Lipids: Total Cholesterol

(Tables 7-10)

Abnormal levels of serum lipids, primarily low density lipoprotein (LDL), high density lipoprotein (HDL), and triglycerides (Tg) have long been recognized as an independent risk factor for cardiovascular disease (CVD). Of interest is whether soy protein and isoflavone consumption would be of value for improving lipid levels as part of a therapeutic lifestyle change, or at least that it would not be detrimental. Recent National Cholesterol Education Program (NCEP) guidelines recommend a goal for fasting total cholesterol of less than 200 mg/dL in all adults with lower levels recommended for people at elevated risk for CVD, including diabetics, smokers, people with hypertension or family history of premature CVD, or beyond middle age.[44]

Study Descriptions

Lipid levels are the most commonly measured CVD risk factor in trials of soy consumption. We found 67 unique randomized trials that met eligibility criteria and reported data on the effect of soy products on lipid levels in at least 10 subjects who consumed soy [not including studies of Lp(a)]; of these 63 reported quantitative data (See Tables 5 and 6).

We found 65 studies that reported on the effect of the consumption of soy products on total cholesterol. Of these, 4 reported only that there was no effect on total cholesterol.[45-48] The remaining 61 studies are described below.[23,24,49-106]

For ease of categorization, we have divided the studies into separate tables as follows: 19 studies investigated dietary soy protein in subjects with abnormal lipids (mean LDL > 130 mg/dL or total cholesterol > 200 mg/dL, Table 7); 22 studies investigated soy protein used as dietary supplements in subjects with abnormal lipids (Table 8); 11 studies investigated pure soy isoflavones in subjects with abnormal lipids (Table 9); 11 studies investigated soy protein in subjects with normolipidemia (Table 10). No studies investigated pure isoflavones in subjects with normolipidemia. Some studies included cohorts of subjects in multiple categories.

The range of daily soy isoflavone intake among studies of soy products with isoflavones was approximately 10 to 185 mg, with a median of 80 mg per day. The range of daily soy protein intake among relevant studies was approximately 14 to 113 g, with a median of 38 g per day. Most studies of hyperlipidemic subjects included post-menopausal women and/or men. The studies of normolipidemic subjects were more likely to include both men and women or be restricted to pre-menopausal women. The large majority of studies were of limited applicability, even within the categories of pre- or post-menopausal women, or men. Only 12 of the studies were graded as being broadly applicable. Among the 61 studies, 5 were rated good quality (A), 32 were rated fair quality (B), and 24 were rated poor quality (C)..

Overall Effect

Across the 61 studies there was a wide range of effects of soy products on total cholesterol, although in most studies the net effect was negative, indicating that compared to control consumption of soy products resulted in reductions in total cholesterol. Approximately two-thirds of the cohorts of subjects consuming soy had a net reduction of total cholesterol compared to control. Across studies, net change ranged from –33 to +7 mg/dL, with the median net change equal to –6 mg/dL. In terms of percent net change (using the baseline level in the soy

intervention cohort as the denominator), net change ranged from approximately –12% to +4%, with a median net change equal to –2.5%.

Soy Product, Dose, Other Variables

Analyses across studies

Figure 2 graphs the net change compared to non-soy control of all cohorts evaluated (that included a non-soy cohort). The left-most graph displays net change in total cholesterol in relationship the baseline total cholesterol level; this graph includes all studies. The middle graph compares net change to daily soy isoflavone consumption (among those studies that report isoflavone content). The right-most graph compares net change to daily soy protein consumption (among those studies that report soy protein content). Study cohorts who consumed soy with isoflavones are indicated by squares; cohorts who consumed soy without isoflavones are indicated by circles; and cohorts who consumed soy isoflavone without soy protein are indicated by triangles. Black symbols represent cohorts where the soy product was consumed as part of the regular diet; open symbols represent cohorts where the soy product was consumed as a supplement to the diet (including soy milk products). Larger symbols indicate cohorts whose mean total cholesterol or LDL was elevated at baseline; smaller symbols indicate cohorts with normal total cholesterol and/or LDL at baseline.

Visual inspection of the graphs reveal no difference across studies in net effect on total cholesterol (as mg/dL or % change) based on baseline total cholesterol levels, amount of soy isoflavones consumed, or amount of soy protein consumed. Likewise, there are no clear differences across studies based on whether the soy products were consumed as part of the diet (i.e., specifically replacing other sources of protein) or as a supplement (consumed in addition to regular diet). Also comparing the net effects of soy protein with isoflavones to soy protein without isoflavones to isoflavones without soy protein reveals similar ranges of effects for all 3 types of products. Because of the relative weakness of total cholesterol as a cardiovascular risk factor as compared to LDL, HDL, and triglycerides, meta-analysis was not performed.

Effect of baseline total cholesterol on net change total cholesterol in individual studies

Three studies performed sub-analyses comparing the effect of soy products on total cholesterol in subjects with different baseline levels. In contrast to the apparent lack of a relationship across studies, all 3 studies – Crouse 1999[51] (Table 7) in a study of hyperlipidemic men and women, Bakhit 1994[72] (Table 8) in a study of mildly hyperlipidemic men, and Lichtenstein 2002[56] (Tables 7 and 9) in a study of men and post-menopausal women – found significantly greater reductions in total cholesterol among the subjects with worse lipid levels (LDL above 166 mg/dL or total cholesterol above 220 mg/dL, or LDL above 160 mg/dL, respectively).

Effect of soy isoflavone dose on net change total cholesterol in individual studies

Fourteen studies[49,51,52,54,56,80-82,86-88,98,102,106] directly compared soy products with different levels of isoflavones, ranging from 0 mg/day to 185 mg/day. Most studies found similar within-cohort or net effects regardless of isoflavone dose. Only 2 studies reported statistically significant differences among cohorts with different isoflavone doses. Gardner 2001[81] (Table 8) found that post-menopausal women who consumed soy protein with 80 mg isoflavones had a decrease in total cholesterol of 10 mg/dL, while those who consumed soy protein without isoflavones had a decrease of only 1 mg/dL; while neither of the changes was statistically different than control, the cohort with higher isoflavone consumption had a significantly greater

reduction than the cohort with lower isoflavone consumption. Crouse 1999[51] (Table 7) also reported a statistically significant relationship between soy isoflavone intake (ranging from 3 mg/day to 62 mg/day) and change in total cholesterol, but only among those men and women with above-median (166 mg/dL) LDL. Among those subjects with less severely abnormal lipids, the trend was not evident.

Effect of soy protein dose on net change total cholesterol in individual studies

Four studies directly compared soy products with different amounts of soy protein.[50,52,56,80] The doses compared ranged from 0 g/day to 55 g/day in women and 71 g/day in men. The conclusions regarding the relative effects of different doses of soy protein were mixed. Both Teixera 2000[52] (Table 7) who compared 4 doses between 20 and 50 mg/day in men, and Tonstad 2002[80] (Table 8) who compared 30 and 50 mg/day in men and post-menopausal women reported no clinically or statistically significant relationship between soy protein dose and effect on total cholesterol. In Potter 1993[50] (Table 7) a greater and more statistically significant effect occurred when the men consumed 50 mg/day of soy protein compared to when they consumed soy flour without protein; however, the study did not report whether the difference among cohorts was statistically significant. Finally, Lichtenstein 2002[56] (Tables 7 and 9) in a study of factorial design in men and post-menopausal women found that the consumption of soy protein significantly decreased total cholesterol (as opposed to the consumption of soy isoflavones).

Effect of soy as diet vs. supplement on net change total cholesterol in individual studies

Only a single study directly compared consumption of soy product as a replacement of dietary protein to soy product as a supplement to usual diet. Verrillo 1985[67] (Tables 7 and 8) found very large reductions in total cholesterol in men and women with very elevated baseline levels; however, the same effect was seen regardless of the mode of soy consumption. Since there was no non-soy control arm, it is difficult to ascertain the explanation for the one-third drop in cholesterol levels.

Effect of sex and menopausal status on net change total cholesterol

Across studies, there was no clear difference in effect evident based on sex or menopausal status of the subjects. Four studies directly compared effects in different populations (data not included in summary tables). Crouse 1999[51] (Table 7) reported that post-menopausal women consuming soy protein with the highest dose of isoflavones (62 mg) had borderline significant reduction (–7%, P=0.06) in total cholesterol in contrast to the pre-menopausal women. Jenkins 2002[49] (Table 7) reported no significant difference in effect between men and women. Both Onning 1998[104] (Table 10) and Teede 2001[77] (Table 8) reported data suggesting no clinical difference in effect between men and women.

Summary

See Section 3.2.6.

Table 7. Effect of soy product diets on total cholesterol (mg/dL) in subjects with hyperlipidemia (Baseline LDL>130 mg/dL or TC>200 mg/dL)

Diet/Supplement	Design	Control	Dose							Change			Net Change [a]			
			mg/day				g/day									
Author Year	Duration	Intervention	Genistein	Daidizein	Glycitein	T Isoflav	Soy Protein	N	Base value	Value	P within	P btw Soy	Value	P vs Control	Population	Applicability Quality
Diet	Xover	Dairy														
Jenkins 2002 12145008	4 wk	ISP w/Isoflavones				73	50	41	261	*-17*		NS	*-9*	<0.01	post♀ ♂	C
		ISP w/Isoflavones				10	52		258	*-18*			*-10*	<0.01		
		Low fat dairy+egg protein							264	*-8*						
Potter 1993	4 wk	ISP + cellulose					50	25	228	*-18*	<0.5	nd	*-26*	<0.01 [b]	♂	C
		ISP + cotyledon					50			*-17*	<0.05		*-25*	<0.01 [b]		
		Soy flour					0			*-11*	NS		*-19*	<0.05 [b]		
		Non-fat dry milk +cellulose								*+8*	NS					
Diet	RCT	Dairy														
Crouse 1999	9 wk	ISP w/Isoflavones				62	25	30	243 [c]	*-10*		NS	*-11*	<0.05	♀♂ (LDL 140-200)	B
		ISP w/Isoflavones				37	25	30	235	*-4*			*-5*	NS		
		ISP w/Isoflavones				27	25	27	248	*-8*			*-9*	NS		
		ISP w/o Isoflavones				3	25	28	239	*-3*			*-4*	NS		
		Casein						31	240	*+1*						
		ISP w/Isoflavones				62	25	15	261 [c]	*-24*		<0.04 Trend	*-24*	<0.03	♀♂ LDL 166-200	
		ISP w/Isoflavones				37	25	12	260	*-20*			*-20*	<0.03		
		ISP w/Isoflavones				27	25	15	264	*-14*			*-14*	NS		
		ISP w/o Isoflavones				3	25	12	261	*-9*			*-9*	NS		
		Casein						16	258	*0*						
		ISP w/Isoflavones				62	25	15	226	*+4*		NS	*+3*	NS	♀♂ LDL 140-166	
		ISP w/Isoflavones				37	25	18	219	*+6*			*+5*	NS		
		ISP w/Isoflavones				27	25	12	229	*-2*			*-3*	NS		
		ISP w/o Isoflavones				3	25	16	223	*+1*			*0*	NS		
		Casein						15	221	*+1*						
Teixeira 2000	6 wk	ISP w/Isoflavones				95	50	15	242	*-8*		nd	*-16*	0.03	♂	A
		ISP w/Isoflavones				76	40	18/17 [d]	230	*-1*			*-9*	NS		
		ISP w/Isoflavones				57	30	18	232	*-4*			*-12*	0.04		
		ISP w/Isoflavones				38	20	15	231	*-4*			*-12*	0.04		
		Calcium caseinate						16	235	*+8*	NS					
Van Horn 2001	6 wk	ISP w/Isoflavones + oats	39	19			19	32	238	-8	< 0.02		*+1*	NS	post♀	B
		Milk+ oats						32	244	-9	< 0.02					
		ISP w/Isoflavones + wheat	39	19			19	31	234	0	NS		*0*	NS		
		Milk+wheat						32	240	0	NS					
Baum 1998	24 wk	ISP w/Isoflavones	35	23	6	90	40	21	250	*-13*		nd	*-6*	NS	post♀	B
		ISP w/o Isoflavones	2	1	2	56	40	23	254	*-15*			*-8*	NS		
		Casein +non-fat dry milk						22	242	*-7*						
Vigna 2000	12 wk	ISP w/Isoflavones				76	40	40	246	*-16*	< 0.01		*0*		post♀	C
		Caseinate						37	253	*-16*	< 0.01					

continued

Table 7. Continued

Diet/Supplement Author Year	Design Duration	Control Intervention	Dose mg/day Genistein	Daidizein	Glycitein	T Isoflav	Dose g/day Soy Protein	N	Base value	Change Value	Change P within	Change P btw Soy	Net Change [a] Value	Net Change [a] P vs Control	Population	Applicability	Quality
Diet	Xover	Animal/Usual															
Lichtenstein 2002 [e]	6 wk	ISP w/Isoflavones	27	14	5	46	55/71 [f]	42	238	*+3*		NS	*-9*	Soy: 0.02 Iso: NS [b]	post♀♂		
		ISP w/o Isoflavones	0.4	0.8	0	1.3	55/71 [f]			*+8*			*-4*				
		Animal w/Isoflavones [e]	27	21	4	52	0			*+10*			*-2*				
		Animal w/o Isoflavones								*+12*							
		ISP w/Isoflavones	27	14	5	46	55/71 [f]	22	nd	258[g]		nd	*-19[b]*	Soy: 0.001 Iso: 0.02 [b]	post♀♂ LDL>160		B
		ISP w/o Isoflavones	0.4	0.8	0	1.3	55/71 [f]			268[g]			*-9[b]*				
		Animal w/Isoflavones [e]	27	21	4	52	0			272[g]			*-5[b]*				
		Animal w/o Isoflavones								277[g]							
		ISP w/Isoflavones	27	14	5	46	55/71 [f]	20	nd	222[g]		nd	*+2[b]*	Soy: NS Iso: NS [b]	post♀♂ LDL<160		
		ISP w/o Isoflavones	0.4	0.8	0	1.3	55/71 [f]			222[g]			*+2[b]*				
		Animal w/Isoflavones [e]	27	21	4	52	0			221[g]			*+1[b]*				
		Animal w/o Isoflavones								220[g]							
Ashton 2000 11194529	4 wk	ISP diet	84	35		120	36	42	224	*-14*			-9	0.03 [b]	♂		C
		Lean meat diet								*-5*							
Azadbakht 2003	7 wk	ISP diet					19	14	201	-13	<0.05		-16	<0.01	♀♂ DM Proteinuria		B
		Usual diet							197	+4	<0.05						
Wong 1998 [h]	5 wk	ISP diet					>15%	13	262	*-15*			*+4*	NS	♂		B
		Animal diet							264	*-11*							
Goldberg 1982	6 wk	ISP diet					91	12	260	*-40*	<0.0001		*-8*	<0.05 [b]	♀♂		B
		Animal diet								*-32*	<0.0001						
Wong 1995	4 wk	ISP diet					>15%	12	273	-41 [j]			*-33*		♂		C
		Animal diet								-8 [j]							
Diet	RCT	Animal/Usual															
Chiechi 2002 11836040	26 wk	ISP diet [k]				47		58/24[d]	236	-9	NS		*+6*	0.07	post♀		C
		Usual diet [k]						55/43 [d]	220	-3	NS						
Shorey 1981	6 wk	ISP diet					55	13	241	-16	0.03		*+6*		♂		C
		Animal diet						11	221	-22	0.002						
Diet	Xover	Miscellaneous															
Jenkins 1999	4 wk	ISP diet					33	31	250	*-27*			-16	<0.001	post♀♂		B
		Vegetarian diet							248	*-10*							
Diet	RCT	Miscellaneous															
Sagara 2004	5 wk	Soy powder baked goods				80	20	25	240	-15	<0.05		*-10*	NS	♂		B
		Usual baked goods						25	232	-5	NS						
Murkies 1995	12 wk	Soy flour						23	235	*-10*	NS		*-1*	NS	post♀		B
		Wheat flour						24	229	*-9*	NS						
Diet	RCT	No Control															
Verrillo 1985 [L]	16 wk	ISP, supplement [L]					31	38	336	-100	<0.01	NS	--		♀♂		B
		ISP, 60 g replacing dietary protein					31	19	340	-100	<0.01		--				
		No control group						--									

Apparent discrepancies between Within-Cohort changes and Between-Cohort changes are due to rounding errors in estimated Within-Cohort changes compared to reported Between-Cohort changes.

[a] Or difference between final values, as noted.
[b] Difference of final values (cross-over study)
[c] Minor discrepancy between text and table. In text baseline value for all subjects reported as 241 mg/dL; within-cohort change the same. In text baseline value for "high-LDL" subjects reported as 260 mg/dL; within-cohort change the same.
[d] N: baseline/final.
[e] Lichtenstein: In both Isoflavone and ISP tables.
[f] Women/Men
[g] Final values. No data on baseline or change from baseline.
[h] Wong 1998: Sub-analyses of same study in LDL<130 and LDL>130 tables.
[j] Graph
[k] No data on how fat content of 2 diets compare.
[L] Verrillo: In both diet and supplement tables

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Table 8. Effect of soy product supplements on total cholesterol (mg/dL) in subjects with hyperlipidemia (Baseline LDL>130 mg/dL or TC>200 mg/dL)

Diet/Supplement	Design	Control	Dose							Change			Net Change [a]				
			mg/day				g/day										
Author Year	Duration	Intervention	Genistein	Daidzein	Glycitein	T Isoflav	Soy Protein	N	Base value	Value	P within	P btw Soy	Value	P vs Control	Population	Applicability	Quality
Supplement	Xover	Dairy															
Bricarello 2004	6 wk	Soy milk[b]	50	33	5	87	25	60	241	*-4*	NS		*-4*	NS	♀♂	👥	C
		Non-fat milk[b]								*0*	NS						
Kurowska 1997	4 wk	Soy milk					31	34	265	*+2*			*-3*	NS	♀♂	👥	B
		Milk, 2% fat								*+5*							
Blum 2003 12659466	6 wk	ISP w/Isoflavones				85	25	24	270	*-30*	0.0001		*+2*	NS [c]	post♀	🧍	C
		Total milk protein								*-32*							
Meyer 2004	5 wk	Soy milk/yogurt				80	30	23	232	*-7*			0	NS [c]	post♀ ♂	🧍	B
		Low fat milk/yogurt								*-7*							
Bakhit 1994	4 wk	ISP + cellulose					25	21	222	*-4*	NS		*-8*	NS [d]	♂	🧍	C
		ISP + cotyledon					25			*0*	NS		*+2*				
		Casein + cellulose								*+4*	NS						
		Casein + cotyledon								*-2*	NS						
		ISP + cellulose					25	11	239	*-16*	<0.05		*-9*	0.04 [d]	♂ TC>220		
		ISP + cotyledon					25			*-19*	<0.05		*-5*				
		Casein + cellulose								*-7*	NS						
		Casein + cotyledon								*-14*	NS						
Sirtori 1999	4 wk	Soy milk	20	11	1	32	35	21	337 [e]	-21 [f]	<0.05		*-12*	<0.05	♀♂	🧍	C
		Milk, high protein								*-9* [g]	NS						
Hermansen 2001	6 wk	ISP w/Isoflavones				>165	50	20	219	*-22*			*-17*	0.08 [h]	♀♂ DM	🧍	C
		Casein							216	*-5*							
Sirtori 2002	4 wk	Soy milk	25	28	24	77	25	20	314	*-6*	NS		*-9*	NS	♀♂	🧍	B
		Milk							318	*+3*	NS						
Cuevas 2003	8 wk	ISP w/Isoflavones	48	24	8	80	<40	18	286	*-46*	<0.05		*+4*	NS [c]	post♀	🧍	B
		Caseinate								*-42*	<0.05						
Supplement	RCT	Dairy															
Teede 2001	13 wk	ISP w/Isoflavones	77	38	5	118	40	86	228	-21	<0.05		*-6*	NS	post♀ ♂	👥	B
		Casein						93	228	-15	<0.05						
Kreijkamp-Kaspers 2004	52 wk	ISP w/Isoflavones	52	41	6		26	88[j]	240	*-1*			+6	NS	post♀	👥	A
		Total milk protein						87[j]	236	*-3*							
Puska 2004	8 wk	ISP w/Isoflavones				153	41	69	291	-16			-15	**<0.001**	post♀ ♂	👥	B
		Yogurt						74	293	-1							

continued

Table 8. Continued

Diet/Supplement	Design	Control	Dose								Change			Net Change [a]				
			mg/day				g/day											
Author Year	Duration	Intervention	Genistein	Daidzein	Glycitein	T Isoflav	Soy Protein	N	Base value	Value	P within	P btw Soy	Value	P vs Control	Population	Applicability	Quality
Supplement	RCT	Dairy															
Tonstad 2002	16 wk	ISP w/Isoflavones				185	50	31	252	*-35*		nd	-9	0.01	post♀ ♂	↑	B
		ISP w/Isoflavones				111	30	34	265	*-33*							
		Casein, 50 g						36	264	*-21*							
		Casein 30 g						29	266	*-30*							
Gardner 2001	12 wk	ISP w/Isoflavones	52	25	4	80	42	31	228	-10		0.03	*-2*	NS	post♀	↑	B
		ISP w/o Isoflavones	2	1	0	3	42	33	228	-1			*+7*	NS			
		Milk protein						30	236	*-8*							
Dent 2001	24 wk	ISP w/Isoflavones				80	40	24	209 [e]	*0*		NS	*0*	NS	peri♀	↑	B
		ISP w/o Isoflavones				4	40	24	217 [e]	*-6*			*-6*				
		Whey protein						21	212 [e]	*0*							
Puska 2002	6 wk	ISP w/Isoflavones				96	52	24	290	-25			-10	0.05	post♀ ♂	↑	C
		Calcium caseinate						28	297	-15							
Supplement	Xover	Miscellaneous															
Jayagopal 2002	12 wk	ISP w/Isoflavones	70	49	13	132	30	31	223	-9	<0.05		*-15*	0.004	post♀ DM	↑	B
		Cellulose							217	+6	NS						
Gardner-Thorpe 2003	6 wk	Soy flour biscuits	45	75		120		19	212	*-8*			0	NS [c]	♂	↑	B
		Wheat flour biscuits								*-8*							
Supplement	Xover	No Control															
Wangen 2001	13 wk	ISP w/Isoflavones	70	47	10	128	53	18	215	*-22*	0.0004	NS [c]	--		post♀	↑	C
		ISP w/Isoflavones	35	24	5	64	53	18/17 [k]		*-24*	0.0004		--				
		ISP w/o Isoflavones	5	4	1	10	53	18		*-18*	0.0006		--				
		No control group						--									
Supplement	RCT	No Control															
Gallagher 2004	39 wk	ISP w/Isoflavones	52	28		96	40	17	221	*+3*	NS	nd	--		post♀	↑	C
		ISP w/Isoflavones	28	20		52	40	19	220	*-7*	NS		--				
		ISP w/o Isoflavones	4	0		4	40	14	213	*0*	NS		--				
		No control group						--									
Mackey 2000 Female study	12 wk	ISP w/Isoflavones				65	28	25	281	*-14*	NS	nd	--		post♀	↑	B
		ISP w/o Isoflavones				4	28	24	288	*-12*			--				
		No control group						--									
Verrillo 1985 [L]	16 wk	ISP, supplement					31	38	336	-100	<0.01	NS	--		♀♂	↑	B
		ISP, 60 g replacing dietary protein [L]					31	19	340	-100	<0.01		--				
		No control group						--									

Apparent discrepancies between Within-Cohort changes and Between-Cohort changes are due to rounding errors in estimated Within-Cohort changes compared to reported Between-Cohort changes.

[a] Or difference between final values, as noted.

[b] Unequal amounts of fat in soy milk (17.5 g/day) and cow milk (0 g/day).

[c] Difference of final values (cross-over study)

[d] Main effect of soy protein

[e] Graph

[f] Reported that 2 soy cross-over arms combined had decrease in total cholesterol of 6.2% (number used in this table), but that first arm had 6.5% reduction and second arm had 7.4% reduction.

[g] Average reduction in 2 milk cross-over arms (-3.9% and –1.6%), assuming baselines were the same for both arms.

[h] *P*=0.004 for difference between final values.

[j] Intention-to-treat analysis (75 completed soy protocol, 78 completed control protocol)

[k] N: baseline/final.

[L] Verrillo: In both diet and supplement tables.

Table 9. Effect of soy isoflavones (without soy protein) on total cholesterol (mg/dL) in subjects with hyperlipidemia (Baseline LDL>130 mg/dL or TC>200 mg/dL)

Diet/Supplement	Design	Control	Dose								Change			Net Change [a]				
			mg/day				g/day											
Author Year	Duration	Intervention	Genistein	Daidzein	Glycitein	T Isoflav	Soy Protein	N	Base value	Value	P within	P btw Soy	Value	P vs Control	Population	Applicability	Quality
Diet	Xover	Animal/Usual															
Lichtenstein 2002 [b]	6 wk	ISP w/Isoflavones [b]	27	14	5	46	55/71 [c]	42	238	*+3*		NS	*-9*	Soy: 0.02 Iso: NS [d]	post♀ ♂	↑	B
		ISP w/o Isoflavones [b]	0.4	0.8	0	1.3	55/71 [c]			*+8*			*-4*				
		Animal w/Isoflavones	27	21	4	52	0			*+10*			*-2*				
		Animal w/o Isoflavones								*+12*							
		ISP w/Isoflavones [b]	27	14	5	46	55/71 [c]	22	nd	258[e]		nd	*-19*[d]	Soy: 0.001 Iso: 0.02 [d]	post♀ ♂ LDL>160		
		ISP w/o Isoflavones [b]	0.4	0.8	0	1.3	55/71 [c]			268[e]			*-9*[d]				
		Animal w/Isoflavones	27	21	4	52	0			272[e]			*-5*[d]				
		Animal w/o Isoflavones								277[e]							
		ISP w/Isoflavones [b]	27	14	5	46	55/71 [c]	20	nd	222[e]		nd	*+2*[d]	Soy: NS Iso: NS [d]	post♀ ♂ LDL<160		
		ISP w/o Isoflavones [b]	0.4	0.8	0	1.3	55/71 [c]			222[e]			*+2*[d]				
		Animal w/Isoflavones	27	21	4	52	0			221[e]			*+1*[d]				
		Animal w/o Isoflavones								220[e]							
Supplement	Xover	Placebo															
Nikander 2004 15240647	13 wk	Isoflavones	6	42	66		0	56	227	+5	NS		*+3*		post♀ Breast CA	↑	A
		Placebo							225	+2	NS						
Nestel 1997	5 wk	Isoflavones	45	35	3	80	0	21	214	*-7*	NS		*+4*		post♀	↑	C
		Placebo								*-11*	NS						
Simons 2000	8 wk	Isoflavones				80	0	20	226	*-16*			*+3*	NS [d]	post♀	↑	B
		Placebo								*-13*							
Supplement	RCT	Placebo															
Han 2002	13 wk	Isoflavones	70	19	11	100	0	40	226	*-27*	<0.001		*-27*	<0.001	post♀	↑	A
		Placebo						40	227	*0*	NS						
Squadrito 2002	26 wk	Genistein	54				0	30	205	*+8*	NS		*+4*	NS	post♀	↑	A
		Placebo						30	208	*+4*	NS						
Petri 2004	26 wk	Soy germ capsules				60	0.8	25	230 [f,g]	*-13*	NS		*-13*		post♀	↑	C [h]
		Lactose capsules						25	204 [f,g]	*0*	NS						
Lissin 2004	6 wk	Isoflavones	44	44	2	90	0	20	243	-5	NS		*+7*	NS	post♀	↑	B
		Placebo						20	236	-12	<0.05						
Dewell 2002	26 wk	Isoflavones	40		50	90	0	20/18 [j]	263	*-15*			*-3*	NS	post♀	↑	C
		Placebo						16	243	*-12*							
Uesugi 2002	4 wk	Isoflavones	0	0	0	62 [k]	0	12	226	*-11*	<0.05		*-14*	NS	peri♀	↑	B
		Placebo						11	238	*+3*	NS						
Uesugi 2003	13 wk	Isoflavones	0	0	0	62 [k]	0	11	224	*-5*			*-4*	NS	post♀	↑	B
		Dextrin						10	221	*-1*							

Apparent discrepancies between Within-Cohort changes and Between-Cohort changes are due to rounding errors in estimated Within-Cohort changes compared to reported Between-Cohort changes.

[a] Or difference between final values, as noted.
[b] Lichtenstein: In both Isoflavone and ISP tables.
[c] Women/Men
[d] Difference of final values (cross-over study)
[e] Final values. No data on baseline or change from baseline.
[f] Significantly different (P<0.05) at baseline.
[g] Graph
[h] In contrast with other outcomes in this article, soy and control ams had significantly different LDL levels.
[j] N: baseline/final.
[k] 31 mg daidzin, 7 mg genistin, 21 mg glycitin

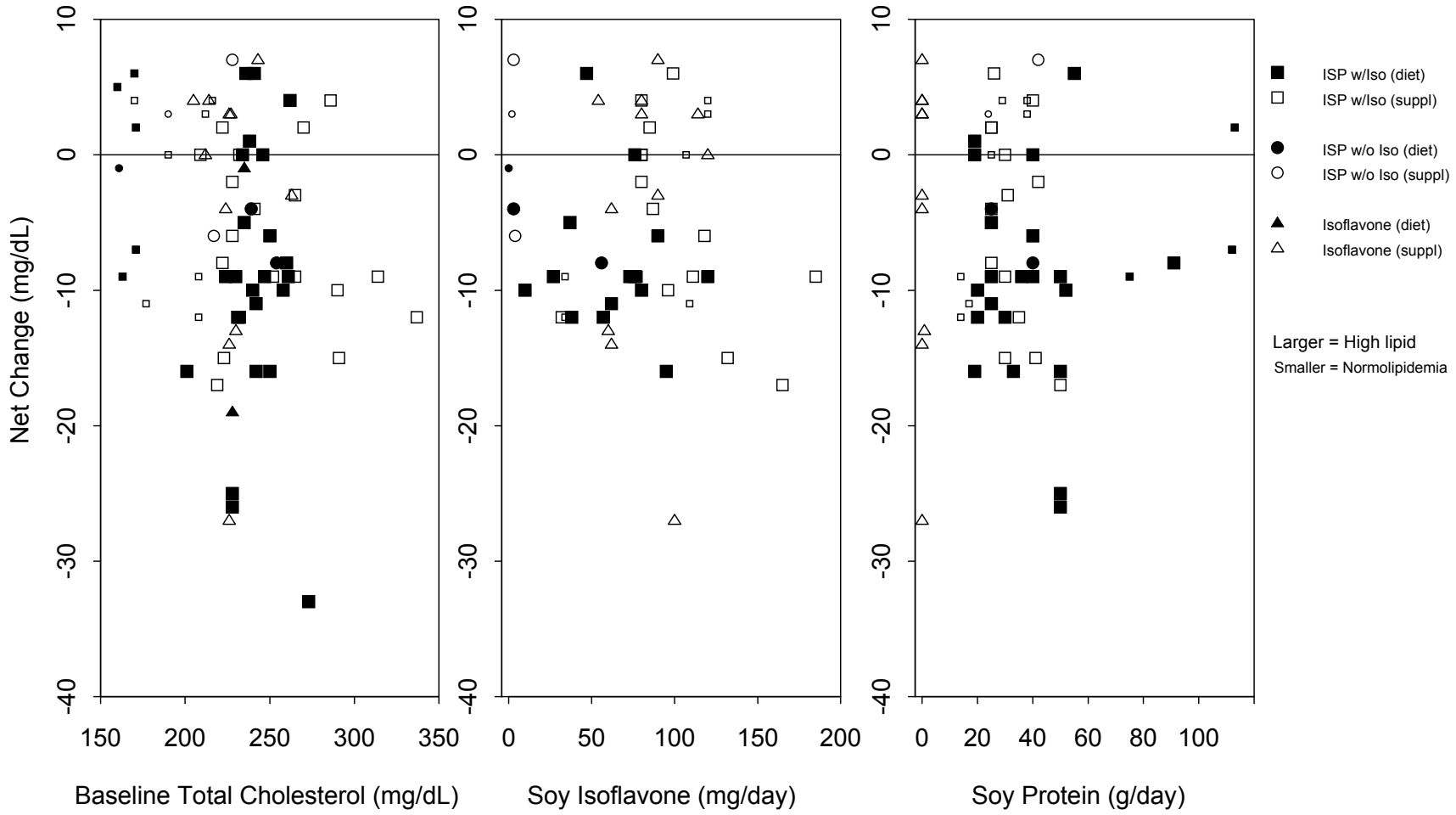
Table 10. Effect of soy products on total cholesterol (mg/dL) in subjects with normolipidemia (Baseline LDL<130 mg/dL or TC<200 mg/dL)

Diet/Supplement	Design	Control	Dose							Change			Net Change [a]				
			mg/day				g/day										
Author Year	Duration	Intervention	Genistein	Daidzein	Glycitein	T Isoflav	Soy Protein	N	Base value	Value	P within	P btw Soy	Value	P vs Control	Population	Applicability	Quality
Diet	Xover	Dairy															
Meinertz 2002	4.5 wk	ISP w/Isoflavones, liquid				2.39/g [b]	20%	1	160	*-29*	<0.001	NS [c]	*+5*	NS [c]	♀♂	↑	C
		ISP w/o Isoflavones, liquid				0.11/g [b]	20%	2	161	*-35*	<0.001		*-1*	NS [c]			
		Casein diet, liquid							155	*-34*	<0.001						
Meinertz 1989	4.5 wk	ISP diet, liquid cholesterol enriched					112	1	171	*-39*			-7	NS [c]	♀♂	↑	C
		Calcium caseinate						1		*-33*							
Meinertz 1988	4 wk	ISP diet, liquid low cholesterol					113	1	171	*-44*			*+2*	NS [c]	♀♂	↑	C
		Casein diet, liquid low cholesterol						0		*-46*							
Diet	Xover	Animal/Usual															
Carroll 1978	~5.5 wk	ISP diet					75	1	163 [d]	*-2*			-9	<0.05 [c]	pre♀	↑	C
		Usual diet						0		*+7*							
Diet	Xover	Miscellaneous															
Wong 1998 [e]	5 wk	ISP diet					>15%	1	170	*-15*			*+6*	NS	♂	↑	B
		Animal diet						3	169	*-9*							
Supplement	Xover	Dairy															
Steinberg 2003	6 wk	ISP w/Isoflavones	55	47	5	107	25	2	190	*-3*		NS	*0*	NS	post♀	↑	C
		ISP w/o Isoflavones	1	0.5	0.5	2	24	4		*0*			*+3*	NS			
		Total milk protein								*-3*							
Supplement	RCT	Dairy															
Murray 2003	26 wk	ISP + Estradiol 0.5 mg	66	44	10	120	38	8	212	*+1*	NS		*+3*	NS	post♀	↑	C
		Total milk protein + Estradiol 0.5 mg						7	211	*-2*	NS						
		ISP + Estradiol 1.0 mg	66	44	10	120	38	8	216	*-13*	NS		*+4*				
		Total milk protein + Estradiol 1.0 mg						7	261 [f]	*-17*	NS						
Supplement	Xover	Miscellaneous															
Washburn 1999	6 wk	ISP w/Isoflavones once daily				34	14	4	208	*-9*		nd	-9	<0.01 [c]	peri♀	↑	B
		ISP w/Isoflavones twice daily				34	14	2		*-12*			-12	<0.01 [c]			
		Carbohydrates								*0*							
Onning 1998	4 wk	Soy milk					23/30 [g]	1	170	-4	NS		*+4*		♀♂	↑	B
		Oat milk						2		-8	NS						
Supplement	RCT	Miscellaneous															
Takatsuka 2000	9 wk	Soy milk				109	17	27	177	*-11*	0.004		-11	0.02	pre♀	↑	B
		No supplement						25	177	*0*	NS						
Supplement	Xover	No Control															
Merz-Demlow 2000	13 wk	ISP w/Isoflavones	70	47	10	128	53	1	144 [h]	*-5*		NS	--		pre♀	↑	C
		ISP w/Isoflavones	35	24	5	64	53	3		*+2*			--				
		ISP w/o Isoflavones	5	4	1	10	53			*+4*			--				
		No control group						--									

Apparent discrepancies between Within-Cohort changes and Between-Cohort changes are due to rounding errors in estimated Within-Cohort changes compared to reported Between-Cohort changes.

[a] Or difference between final values, as noted.
[b] Per gram protein. No data on number of grams of protein.
[c] Difference of final values (cross-over study)
[d] Calculated mean of graphically displayed values for each cross-over arm. “Final” results are mean value of levels measured twice weekly.
[e] Wong 1998: Sub-analyses of same study in LDL<130 and LDL>130 tables.
[f] Significantly higher at baseline than other study arms because of single outlier with hypertriglyceridemia.
[g] Women/Men
[h] Measurements made at 4 menstrual cycle phases: early follicular, midfollicular, periovulatory, midluteal. Data extracted for periovulatory only. LDL change was greatest during this phase in high isoflavone group.

Figure 2. Net change of total cholesterol with soy product consumption compared to control, by baseline level, isoflavone content, and soy protein content. Studies without non-soy control are not included. Studies without data on isoflavone or protein content are omitted from relevant graphs. ISP w/Iso = soy protein with isoflavones; ISP w/o Iso = soy protein without isoflavones; suppl = supplement.



3.2.3. Lipids: Low Density Lipoprotein

(Tables 11-15, Figures 3-5)

Study Descriptions

We found 55 studies that reported on the effect of the consumption of soy products on low density lipoprotein (LDL). Of these, 3 reported only that there was no effect on LDL.[46-48] The remaining 52 studies are described below. [23,24,49-51,53,55-60,62,64,67-94,96,98-100,102-106]

For ease of categorization, we have divided the studies into separate tables as follows: 13 studies investigated dietary soy protein in subjects with elevated LDL (mean >130 mg/dL, Table 11); 22 studies investigated soy protein used as dietary supplements in subjects with elevated LDL (Table 12); 9 studies investigated pure soy isoflavones in subjects with elevated LDL (Table 13); 10 studies investigated soy protein in subjects with normolipidemia (Table 14). No studies investigated pure isoflavones in subjects with normolipidemia. Some studies included cohorts of subjects in multiple categories.

The range of daily soy isoflavone intake among studies of soy products with isoflavones was approximately 10 to 185 mg, with a median of 80 mg per day. The range of daily soy protein intake among relevant studies was approximately 14 to 113 g, with a median of 34 g per day. Most studies of hyperlipidemic subjects included post-menopausal women and/or men. The studies of normolipidemic subjects were more likely to include both men and women or be restricted to pre-menopausal women. The large majority of studies were of limited applicability, even within the categories of pre- or post-menopausal women, or men. Only 11 of the studies were graded as being broadly applicable. Among the 52 studies, 4 were rated good quality (A), 28 were rated fair quality (B), and 20 were rated poor quality (C).

Overall Effect

Across the 52 studies there was a wide range of effects of soy products on LDL, although in most studies the net effect was negative, indicating that compared to control consumption of soy products resulted in reductions in LDL. Approximately three-quarters of the cohorts of subjects consuming soy had a net reduction of LDL compared to control (Figure 3). Across studies, net change ranged from –32 to +13 mg/dL, with the median net change equal to –5 mg/dL. In terms of percent net change (using the baseline level in the soy intervention cohort as the denominator), net change ranged from approximately –21% to +9%, with a median net change equal to –3%.

The summary estimate from a random-effects model meta-analysis of all soy cohorts with a non-soy control was statistically significant (Figure 4); the net change in LDL was –5 (95% confidence interval [CI] –7 to –3) mg/dL, where the adjusted summary mean baseline LDL was approximately 150 mg/dL. This finding is in agreement with a recent meta-analysis of the effect of soy products on LDL and HDL by Weggemans et al. (2003)[107], who reported a net change in LDL of –7 (95% CI –10, –3) mg/dL. Our primary meta-analysis differed in that we used looser criteria for inclusion – thus we included about 3 times as many studies. Both of these meta-analyses differ markedly from an early meta-analysis by Anderson et al. (1995)[1] which reported a summary net change of –22 (95 % CI –32, –11) mg/dL. However, that meta-analysis used much looser inclusion criteria, including non-randomized trials, studies of children, very small sample sizes, and short intervention durations. Their findings were highly affected by several non-randomized trials and the inclusion of Verrillo 1985[67] (Tables 11 and 12), a study that lacked randomization to a non-soy control.

Soy Product, Dose, Other Variables

Analyses across studies

Figure 3 graphs the net change compared to non-soy control of all cohorts evaluated (that included a non-soy cohort). In a similar manner as the total cholesterol graph, the left-most graph displays net change in LDL in relationship the baseline LDL; this graph includes all studies. The middle graph compares net change to daily soy isoflavone consumption (among those studies that report isoflavone content). The right-most graph compares net change to daily soy protein consumption (among those studies that report soy protein content). Adjusted regression lines are included.

We ran separate regressions of mean baseline LDL, total soy isoflavones consumed, and total soy protein consumed against net change LDL for studies with abnormal baseline LDL (Table 15). The regressions were adjusted using a random effects model technique; thus studies without sufficient data to estimate net change variance were excluded. Multivariate and univariate analyses were performed for the 3 covariates. Sub-analyses were also performed for studies with abnormal mean baseline LDL (>130 mg/dL) to focus on the effect on those people with hyperlipidemia. As appropriate, sub-analyses were also performed for consumption of isoflavones alone (without soy protein) and soy protein with isoflavones. Because of the small number of such studies, soy protein without isoflavones was not analyzed separately.

All multivariate analyses performed resulted in non-significant associations between the included covariates and net change LDL. Among the numerous univariate meta-regressions performed, only soy protein dose was statistically significantly associated with net change LDL, but only in the sub-group of studies with abnormal baseline LDL (Table 15 and Figure 3, left). Across studies, for each additional 10 grams of soy protein consumed per day, the average net reduction of LDL was 1.4 (95% CI 0.0, 2.7) mg/dL greater. Inclusion of studies with lower baseline LDL reduced the degree and significance of the association.

Furthermore, inclusion either of only studies with soy protein (dose >10 g/day) or only studies of protein with isoflavones yielded no association between protein dose and net change LDL. Excluding either soy protein with isoflavone studies of lower baseline LDL or the few outlier studies of higher protein dose (>80 g/day) yielded similar trends toward an association between higher dose soy protein and greater net reduction of LDL.

Evaluation of the effect of baseline LDL on net change LDL across studies revealed no association; however in sub-group of studies with elevated LDL (within the range of about 135 to 200 mg/dL), there was a trend suggesting that for studies with mean baseline LDL 10 mg/dL higher than other studies, the average net LDL reduction was 1.4 (95% CI 0, 2.8) mg/dL greater. This trend was similar for studies of protein with isoflavones and higher baseline LDL levels, but not for studies of isoflavones alone. No meta-regression analysis found an association between soy isoflavone dose and net change LDL.

These analyses, however, are subject to biases due to analyzing mean values across studies. In addition, these analyses are combining data from a very heterogeneous group of studies in regards to subject populations, soy products, and controls, among other factors. In all analyses, the studies were found to be statistically significantly heterogeneous. Associations may be either exaggerated or minimized because of the heterogeneity.

We also performed meta-analyses of sub-groups of studies based on study quality, baseline LDL, type of soy product, and soy diet versus soy supplement (Figure 5). All sub-group meta-analyses were grossly similar. While the studies rated of poor quality did, on average, find a larger effect of soy products than better quality studies, the difference in effects was not

statistically significantly different (P=0.2). Of note, the studies that evaluated soy isoflavones without soy protein had a high degree of heterogeneity with mean net changes in LDL ranging from –32 mg/dL to +13 mg/dL (or +42 mg/dL in the subset of women with elevated baseline LDL).

Effect of baseline LDL on net change LDL in individual studies

The 4 studies that performed sub-analyses comparing the effect of soy products on LDL in subjects with different baseline levels came to a different conclusions. Crouse 1999[51] (Table 11) found a greater benefit (with higher isoflavone-dose) in a study of hyperlipidemic men and women with above median LDL (166 mg/dL). Lichtenstein 2002[56] (Tables 11 and 13) in a study of men and post-menopausal women also found a larger, significant effect among those with elevated LDL (>160 mg/dL) in contrast to those with lower LDL. Bakhit 1994[72] (Table 12) in a study of mildly hyperlipidemic men found essentially the same effect among those with elevated total cholesterol (>220 mg/dL) as the whole cohort. Nikander 2004[89] (Table 13) in a study of post-menopausal women with a history of treated breast cancer found that the sub-group of women who had above median LDL (162 mg/dL) soy isoflavone consumption resulted in a statistically significant *increase* in LDL. This was in contrast to a smaller, non-significant net increase for the cohort as a whole.

Effect of soy isoflavone dose on net change LDL in individual studies

Twelve studies[49,51,56,80-82,86-88,98,102,106] directly compared soy products with different levels of isoflavones, ranging from 0 mg/day to 185 mg/day. Most studies found similar within-cohort or net effects regardless of isoflavone dose. Only 4 studies reported statistically significant differences among cohorts with different isoflavone doses. Gardner 2001[81] (Table 12) found that post-menopausal women who consumed soy protein with 80 mg isoflavones had a decrease in LDL of 15 mg/dL while those who consumed soy protein without isoflavones had a decrease of only 3 mg/dL; while neither of the changes was statistically different than control, the cohort with higher isoflavone consumption had a significantly greater reduction than the cohort with lower isoflavone consumption. Crouse 1999[51] (Table 11) reported a statistically significant relationship between soy isoflavone intake (ranging from 3 mg/day to 62 mg/day) and change in LDL, but only among those men and women with above-median (166 mg/dL) LDL. Among those subjects with less severely elevated LDL, the trend was not evident, although the effect was greatest in the high isoflavone cohort. In a cross-over study, Merz-Demlow 2000[106] (Table 14) compared 3 soy supplements with different levels of isoflavones in pre-menopausal, normolipidemic women. Only during the period where the women consumed the highest isoflavone supplement did their LDL levels fall, by an amount significantly different than changes during consumption of the other, lower isoflavone, periods. Similarly, Wangen 2001[86] (Table 12) in a cross-over study of 3 soy supplements with different levels of isoflavone in post-menopausal women found progressively greater decreases in LDL during periods with higher isoflavone consumption. Of note, a meta-regression performed by Weggemans et al. (2003)[107] found no dose-response relation between changes in soy isoflavone intake and changes in LDL.

Meta-analysis of studies comparing 2 or more soy products with different levels of isoflavones

We performed random effects model meta-analyses of the 11 studies that reported sufficient data comparing 2 or more soy products with different levels of isoflavones.[49,51,56,81,82,86-88,98,102,106] In one analysis we included all cohorts with soy protein. This analysis is faulty in that it allows comparison of multiple high-isoflavone cohorts to the same low-

isoflavone cohort, thus breaking the assumption of independence between all studies. Nevertheless, the summary net difference in effect on LDL was small and non-significant at –3 (95% CI –6, +1) mg/dL. In a second analysis, where we compared only the highest isoflavone dose cohort to the lowest, the net difference was similarly small and non-significant at –3 (95 % CI –8, +1) mg/dL. These results are in contrast to a recently published meta-analysis by Zhuo et al. (2004)[43] largely because of the addition of the recently published Gallagher 2004[87] and Dent 2001,[82] which was excluded because of a too long study duration, and Meinertz 2002,[98] which might have been excluded because the amount of isoflavones is poorly reported. Importantly, all these studies found no difference in effect.

Effect of soy protein dose on net change LDL in individual studies

Three studies directly compared soy products with different amounts of soy protein.[56,80,108] The doses compared ranged from 0 g/day to 55 g/day in women and 71 g/day in men. Two of the 3 studies reported a difference in effect based on level of soy protein consumption. In Potter 1993[50] (Table 11) a greater and more statistically significant effect occurred when the men consumed 50 mg/day of soy protein compared to when they consumed soy flour without protein; however, the study did not report whether the difference among cohorts was statistically significant. Lichtenstein 2002[56] (Tables 11 and 13) in a study of factorial design in men and post-menopausal women found that the consumption of soy protein significantly decreased LDL (as opposed to the consumption of soy isoflavones). In contrast, Tonstad 2002[80] (Table 12) who compared 30 and 50 mg/day in men and post-menopausal women reported no clinically or statistically significant relationship between soy protein dose and effect on LDL. Weggemans et al. (2003)[107] also found no association between dose of soy protein consumption and change in LDL.

Effect of soy as diet vs. supplement on net change LDL in individual studies

Only a single study directly compared consumption of soy product as a replacement of dietary protein to soy product as a supplement to usual diet. Verrillo 1985[67] (Tables 11 and 12) found very large reductions in LDL in men and women with very elevated baseline levels; however, the same effect was seen regardless of the mode of soy consumption. Since there was no non-soy control arm, it is difficult to ascertain the explanation for the greater than one-third drop in LDL levels. Meta-analysis of the dietary soy products alone (Figure 5) yielded a summary net change in LDL of –7 (95% CI –9, –4) mg/dL, which was somewhat greater than the net change among the soy supplements studies, –4 (95% CI –7, –1) mg/dL.

Effect of sex and menopausal status on net change LDL

Across studies, there was no clear difference in effect evident based on sex or menopausal status of the subjects. Four studies directly compared effects in different populations (data not included in summary tables). Crouse 1999[51] (Table 11) reported that post-menopausal women consuming soy protein with the highest dose of isoflavones (62 mg) had borderline significant reduction (–8%, P=0.07) in LDL in contrast to the pre-menopausal women. Jenkins 2002[49] (Table 11) reported no significant difference in effect between men and women. Both Onning 1998[104] (Table 14) and Teede 2001[77] (Table 12) reported data suggesting no clinical difference in effect between men and women.

Summary

See Section 3.2.6.

Table 11. Effect of soy product diets on low density lipoprotein (mg/dL) in subjects with hyperlipidemia (Baseline LDL>130 mg/dL)

Diet/Supplement	Design	Control	Dose								Change			Net Change [a]				
			mg/day				g/day											
Author Year	Duration	Intervention	Genistein	Daidzein	Glycitein	T Isoflav	Soy Protein	N	Base value		Value	P within	P btw Soy	Value	P vs Control	Population	Applicability	Quality
Diet	Xover	Dairy																
Jenkins 2002 12145008	4 wk	ISP w/Isoflavones				73	50	41	176		*-16*		NS	*-10*	<0.01	post♀ ♂	👫	C
		ISP w/Isoflavones				10	52		175		*-13*			*-7*	<0.01			
		Low fat dairy+egg protein							178		*-6*							
Potter 1993	4 wk	ISP + cellulose					50	24	175		*-14*	NS	nd	*-18*	<0.01 [b]	♂	🚹	C
		ISP + cotyledon					50				*-15*	<0.05		*-19*	<0.01 [b]			
		Soy flour					0				*-9*	NS		*-13*	NS [b]			
		Non-fat dry milk+cellulose									*+4*	NS						
Diet	RCT	Dairy																
Crouse 1999	9 wk	ISP w/Isoflavones				62	25	30	166 [c]		*-10*		NS	*-10*	<0.05	♀♂ (LDL 140-200)	👫	B
		ISP w/Isoflavones				37	25	30	161		*-5*			*-5*	NS			
		ISP w/Isoflavones				27	25	28	170		*-5*			*-4*	NS			
		ISP w/o Isoflavones				3	25	27	164		*-4*			*-5*	NS			
		Casein						31	165		*0*							
		ISP w/Isoflavones				62	25	15	185 [c]		*-22[c]*		<0.04 Trend	*-20[c]*	<0.03	♀♂ LDL 166-200		
		ISP w/Isoflavones				37	25	12	182		*-17*			*-15*	<0.03			
		ISP w/Isoflavones				27	25	12	186		*-12*			*-10*	NS			
		ISP w/o Isoflavones				3	25	15	185		*-10*			*-8*	NS			
		Casein						16	182		*-2*							
		ISP w/Isoflavones				62	25	15	147		*+1*		NS	*-2*	NS	♀♂ LDL 140-166		
		ISP w/Isoflavones				37	25	16	146		*+4*			*+1*	NS			
		ISP w/Isoflavones				27	25	18	150		*+4*			*+1*	NS			
		ISP w/o Isoflavones				3	25	12	148		*+1*			*-2*	NS			
		Casein						15	146		*+3*							
Van Horn 2001	6 wk	ISP w/Isoflavones + oats	39	19			19	32	150		-10	<0.02		*-1*		post♀	👫	B
		Milk+ oats						32	155		-9	<0.02						
		ISP w/Isoflavones + wheat	39	19			19	31	147		0	NS		*+1*				
		Milk + wheat						32	151		-1	NS						
Vigna 2000	12 wk	ISP w/Isoflavones				76	40	40	159		*-14*	<0.01		*-2*		post♀	👫	C
		Caseinate						37	167		*-12*	<0.01						

continued

Table 11. Continued

Diet/Supplement	Design	Control	Dose								Change			Net Change [a]				
			mg/day				g/day											
Author Year	Duration	Intervention	Genistein	Daidzein	Glycitein	T Isoflav	Soy Protein	N	Base value	Value	P within	P btw Soy	Value	P vs Control	Population	Applicability	Quality
Diet	Xover	Animal/Usual															
Lichtenstein 2002 [d]	6 wk	ISP w/Isoflavones	27	14	5	46	55/71 [e]	42	160	*+6*		<0.05	*-5*	Soy: 0.04 Iso: NS [b]	post♀♂	↑	B
		ISP w/o Isoflavones	0.4	0.8	0	1.3	55/71 [e]			*+8*			*-3*				
		Animal w/Isoflavones [d]	27	21	4	52	0			*+12*			*+1*				
		Animal w/o Isoflavones								*+11*							
		ISP w/Isoflavones	27	14	5	46	55/71 [e]	22	>160	181 [f]		nd	*-14[b]*	Soy: 0.003 Iso: NS [d]	post♀♂ LDL>160	↑	B
		ISP w/o Isoflavones	0.4	0.8	0	1.3	55/71 [e]			186 [f]			*-9[b]*				
		Animal w/Isoflavones [d]	27	21	4	52	0			192 [f]			*-3[b]*				
		Animal w/o Isoflavones								195 [f]							
		ISP w/Isoflavones	27	14	5	46	55/71 [e]	20	<160	148 [f]		nd	*+5[b]*	Soy: NS Iso: NS [d]	post♀♂ LDL<160		
		ISP w/o Isoflavones	0.4	0.8	0	1.3	55/71 [e]			147 [f]			*+4[b]*				
		Animal w/Isoflavones [d]	27	21	4	52	0			149 [f]			*+6[b]*				
		Animal w/o Isoflavones								143 [f]							
Ashton 2000 10694766	4 wk	ISP diet	84	35		120	36	42	142	*-8*	<0.05		+3	<0.05 [b]	♂	↑	B
		Lean meat diet								*-5*	NS						
Azadbakht 2003	7 wk	ISP diet					19	14	145	-6	<0.05		-8	<0.04	♀♂ DM Proteinuria	↑	B
		Usual diet							144	+2	NS						
Wong 1998 [g]	5 wk	ISP diet					>15%	13	181	*-23*			*-9*	0.03	♂	↑	B
		Animal diet							182	*-14*							
Goldberg 1982	6 wk	ISP diet					91	12	191	*-33*	<0.0001		*-10*	<0.05 [b]	♀♂	↑	B
		Animal diet								*-23*	<0.001						
Diet	RCT	Animal/Usual															
Chiechi 2002 11836040	26 wk	ISP diet[h]				47		58/24 [j]	159	-6	NS		*-6*		post♀	↑	C
		Usual diet[h]						55/43 [j]	145	0	NS						
Diet	Xover	Miscellaneous															
Jenkins 1999	4 wk	ISP diet					33	31	170	*-21*			-11	<0.001	post♀♂	↑	B
		Vegetarian diet							169	*-9*							
Diet	RCT	No Control															
Verrillo 1985 [k]	16 wk	ISP, supplement [k]					31	38	243	-89	<0.01	NS	--		♀♂	↑	B
		ISP, 60 g replacing dietary protein					31	19	259	-100	<0.01		--				
		No control group						--									

Apparent discrepancies between Within-Cohort changes and Between-Cohort changes are due to rounding errors in estimated Within-Cohort changes compared to reported Between-Cohort changes.

[a] Or difference between final values, as noted.
[b] Difference of final values (cross-over study)
[c] Minor discrepancy between text and table. In text baseline value for all subjects reported as 165 mg/dL; within-cohort change the same. In text baseline value for "high-LDL" subjects reported as 181 mg/dL; within-cohort change reported as –18 mg/dL, implying a net change of –16 mg/dL.
[d] Lichtenstein: In both Isoflavone and ISP tables.
[e] Women/Men
[f] Final values. No data on baseline or change from baseline.

[g] Wong 1998: Sub-analyses of same study in LDL<130 and LDL>130 tables.
[h] No data on how fat content of 2 diets compare.
[j] N: baseline/final.
[k] Verrillo: In both diet and supplement tables.

Table 12. Effect of soy product supplements on low density lipoprotein (mg/dL) in subjects with hyperlipidemia (Baseline LDL>130 mg/dL)

Diet/Supplement	Design	Control	Dose							Change			Net Change [a]				
			mg/day				g/day										
Author Year	Duration	Intervention	Genistein	Daidizein	Glycitein	T Isoflav	Soy Protein	N	Base value	Value	P within	P btw Soy	Value	P vs Control	Population	Applicability	Quality
Supplement	Xover	Dairy															
Bricarello 2004	6 wk	Soy milk[b]	50	33	5	87	25	60	157	*-9*			*-10*	<0.05	♀♂	👥	C
		Non-fat milk[b]								*+1*							
Kurowska 1997	4 wk	Soy milk					31	34	172	*-7*			*-4*	NS	♀♂	👥	B
		Milk, 2% fat								*-3*							
Blum 2003 12659466	6 wk	ISP w/Isoflavones				85	25	24	178	*-36*	<0.0001		*+5*	NS [c]	post♀	🧍	C
		Total milk protein								*-41*							
Meyer 2004	5 wk	Soy milk/yogurt				80	30	23	159	*-8*			-2	NS [c]	post♀ ♂	🧍	B
		Low fat milk/yogurt								*-6*							
Bakhit 1994	4 wk	ISP + cellulose					25	21	158	-3	NS		*-8*	NS [d]	♂	🧍	C
		ISP + cotyledon					25			0	NS		*+2*				
		Casein + cellulose								5	NS						
		Casein + cotyledon								-2	NS						
		ISP + cellulose					25	11	169	-9	NS		*-8*	0.07 [d]	♂ TC>220		
		ISP + cotyledon					25			-11	NS		*-1*				
		Casein + cellulose								-1	NS						
		Casein + cotyledon								-10	NS						
Sirtori 1999	4 wk	Soy milk	20	11	1	32	35	21	247 [e]	-19	<0.05		*-11*	<0.05	♀♂	🧍	C
		Milk, high protein								*-8*	NS						
Hermansen 2001	6 wk	ISP w/Isoflavones				>165	50	20	140	*-24*			*-12*	0.048 [f]	♀♂ DM	🧍	C
		Casein							141	*-12*							
Sirtori 2002	4 wk	Soy milk	25	28	24	77	25	20	226	*+7*	NS		*-3*	NS	♀♂	🧍	B
		Milk							225	*+10*	NS						
Cuevas 2003	8 wk	ISP w/Isoflavones	48	24	8	80	<40	18	195	*-35*	<0.05		*-1*	NS [c]	post♀	🧍	B
		Caseinate								*-34*	<0.05						
Supplement	RCT	Dairy															
Teede 2001	13 wk	ISP w/Isoflavones	77	38	5	118	40	86	151	-16	<0.05		*-5*	NS	post♀ ♂	👥	B
		Casein						93	147	-11	<0.05						
Kreijkamp-Kaspers 2004	52 wk	ISP w/Isoflavones	52	41	6		26	88[g]	161	*-1*			+5		post♀	👥	A
		Total milk protein						87[g]	159	*-6*							
Puska 2004	8 wk	ISP w/Isoflavones				153	41	69	197	-14			-15	<0.001	post♀ ♂	👥	B
		Yogurt						74	198	+2							
Tonstad 2002	16 wk	ISP w/Isoflavones				185	50	31	177	*-37*		nd	-10	0.01	post♀ ♂	👥	B
		ISP w/Isoflavones				111	30	34	186	*-34*							
		Casein, 50 g						29	192	*-30*							
		Casein 30 g						36	188	*-21*							
Gardner 2001	12 wk	ISP w/Isoflavones	52	25	4	80	42	31	151	-15		0.01	*-3*	NS	post♀	👥	B
		ISP w/o Isoflavones	2	1	0	3	42	33	151	-3			*+9*	NS			
		Milk protein						30	154	*-12*							

continued

Table 12. Continued.

Diet/Supplement / Author Year	Design / Duration	Control / Intervention	Dose mg/day Genistein	Daidzein	Glycitein	T Isoflav	Dose g/day Soy Protein	N	Base value	Change Value	Change P within	Change P btw Soy	Net Change [a] Value	Net Change [a] P vs Control	Population	Applicability	Quality
Supplement	RCT	Dairy															
Dent 2001	24 wk	ISP w/Isoflavones				80	40	24	127 [e]	*+6*		NS	*+4*	NS	peri♀	👪	B
		ISP w/o Isoflavones				4	40	24	135 [e]	*+1*			*-1*				
		Whey protein						21	134 [e]	*+2*							
Puska 2002	6 wk	ISP w/Isoflavones				96	52	24	198	-26			-10	<0.05	post ♀♂	🧍	C
		Calcium caseinate						28	199	-16							
Supplement	Xover	Miscellaneous															
Jayagopal 2002	12 wk	ISP w/Isoflavones	70	49	13	132	30	31	140	-10	<0.05		*-17*	0.001	post ♀ DM	👪	B
		Cellulose							134	+7	0.05						
Gardner-Thorpe 2003	6 wk	Soy flour biscuits	45	75		120		19	139	*-4*			+6	NS [c]	♂	🧍	B
		Wheat flour biscuits								*-10*							
Supplement	Xover	No Control															
Wangen 2001	13 wk	ISP w/Isoflavones	70	47	10	128	53	18	136	*-20*	0.0003	0.02 [c]	--		post ♀	👪	C
		ISP w/Isoflavones	35	24	5	64	53	18/17 [h]		*-18*	0.0006	0.07 [c]	--				
		ISP w/o Isoflavones	5	4	1	10	53	18		*-12*	0.02	--	--				
		No control group						--									
Supplement	RCT	No Control															
Gallagher 2004	39 wk	ISP w/Isoflavones	52	28		96	40	17	141	*+3*	NS	nd	--		post ♀	👪👪	C
		ISP w/Isoflavones	28	20		52	40	19	138	*+3*	NS		--				
		ISP w/o Isoflavones	4	0		4	40	14	134	*-1*	NS		--				
		No control group						--									
Mackey 2000 Female study	12 wk	ISP w/Isoflavones				65	28	25	196	*-14*	0.04	nd	--		post ♀	👪	B
		ISP w/o Isoflavones				4	28	24	197	*-13*			--				
		No control group						--									
Verrillo 1985 [j]	16 wk	ISP, supplement					31	38	243	-89	<0.01	NS	--		♀♂	👪👪	B
		ISP, 60 g replacing dietary protein [j]					31	19	259	-100	<0.01		--				
		No control group						--									

Apparent discrepancies between Within-Cohort changes and Between-Cohort changes are due to rounding errors in estimated Within-Cohort changes compared to reported Between-Cohort changes.

[a] Or difference between final values, as noted.
[b] Unequal amounts of fat in soy milk (17.5 g/day) and cow milk (0 g/day).
[c] Difference of final values (cross-over study)
[d] Main effect of soy protein
[e] Graph
[f] *P*=0.004 for difference between final values.
[g] Intention-to-treat analysis (75 completed soy protocol, 78 completed control protocol)
[h] N: baseline/final.
[j] Verrillo: In both diet and supplement tables.

Table 13. Effect of soy isoflavones (without soy protein) on low density lipoprotein (mg/dL) in subjects with hyperlipidemia (Baseline LDL>130 mg/dL)

Diet/Supplement	Design	Control	Dose							Change			Net Change [a]				
			mg/day				g/day										
Author Year	Duration	Intervention	Genistein	Daidzein	Glycitein	T Isoflav	Soy Protein	N	Base value	Value	P within	P btw Soy	Value	P vs Control	Population	Applicability	Quality
Diet	Xover	Animal/Usual															
Lichtenstein 2002 [b]	6 wk	ISP w/Isoflavones [b]	27	14	5	46	55/71 [c]	42	160	*+6*		<0.05	*-5*	Soy: 0.04 Iso: NS [d]	post♀ ♂	⬆	B
		ISP w/o Isoflavones [b]	0.4	0.8	0	1.3	55/71 [c]			*+8*			*-3*				
		Animal w/Isoflavones	27	21	4	52	0			*+12*			*+1*				
		Animal w/o Isoflavones								*+11*							
		ISP w/Isoflavones [b]	27	14	5	46	55/71 [c]	22	>160	181[e]		nd	*-14[d]*	Soy: 0.003 Iso: NS [d]	post♀ ♂ LDL>160	⬆	B
		ISP w/o Isoflavones [b]	0.4	0.8	0	1.3	55/71 [c]			186[e]			*-9[d]*				
		Animal w/Isoflavones	27	21	4	52	0			192[e]			*-3[d]*				
		Animal w/o Isoflavones								195[e]							
		ISP w/Isoflavones [b]	27	14	5	46	55/71 [c]	20	<160	148[e]		nd	*+5[d]*	Soy: NS Iso: NS [d]	post♀ ♂ LDL<160		
		ISP w/o Isoflavones [b]	0.4	0.8	0	1.3	55/71 [c]			147[e]			*+4[d]*				
		Animal w/Isoflavones	27	21	4	52	0			149[e]			*+6[d]*				
		Animal w/o Isoflavones								143[e]							
Supplement	Xover	Placebo															
Nikander 2004 15240647	13 wk	Isoflavones	6	42	66		0	56	149	+11	NS		*+13*	NS	post♀ Breast CA		
		Placebo							147	-2	NS						
		Isoflavones	6	42	66		0	28	>162	+25			*+42*	0.009	post♀ Breast CA LDL>162	⬆	A
		Placebo								-17							
Nestel 1997	5 wk	Isoflavones	45	35	3	80	0	21	138	*-5*	NS		*+3*		post♀	⬆	C
		Placebo								*-8*	NS						
Simons 2000	8 wk	Isoflavones				80	0	20	152	*-13*			*-3*	NS [d]	post♀	⬆	B
		Placebo								*-10*							
Supplement	RCT	Placebo															
Han 2002	13 wk	Isoflavones	70	19	11	100	0	40	134	*-13*	*<0.001*		*-19*	<0.001	post♀	⬆	A
		Placebo					0	40	134	*+6*	NS						
Squadrito 2002	26 wk	Genistein	54				0	30	139	*0*	NS		*+4*	NS	post♀	⬆	A
		Placebo						30	147	*-4*	NS						
Petri 2004	26 wk	Soy germ capsules				60	0.8	25	152 [f,g]	*-20*	<0.05		*-32*		post♀	⬆	C [h]
		Lactose capsules						25	131 [f,g]	*+12*	NS						
Lissin 2004	6 wk	Isoflavones	44	44	2	90	0	20	163	-1	NS		*+8*	NS	post♀	⬆	B
		Placebo						20	165	-9	<0.05						
Uesugi 2002	4 wk	Isoflavones	0	0	0	62 [j]	0	12	148	*-10*	<0.05		*-12*	NS	peri♀	⬆	B
		Placebo						11	162	*+2*	NS						

Apparent discrepancies between Within-Cohort changes and Between-Cohort changes are due to rounding errors in estimated Within-Cohort changes compared to reported Between-Cohort changes.

[a] Or difference between final values, as noted.
[b] Lichtenstein: In both Isoflavone and ISP tables.
[c] Women/Men
[d] Difference of final values (cross-over study)
[e] Final values. No data on baseline or change from baseline.
[f] Significantly different (P<0.05) at baseline.
[g] Graph
[h] In contrast with other outcomes in this article, soy and control ams had significantly different LDL levels.
[j] 31 mg daidzin, 7 mg genistin, 21 mg glycitin

Table 14. Effect of soy products on low density lipoprotein (mg/dL) in subjects with normolipidemia (Baseline LDL<130 mg/dL)

Diet/Supplement	Design	Control	Dose							Change			Net Change [a]				
			mg/day				g/day										
Author Year	Duration	Intervention	Genistein	Daidizein	Glycitein	T Isoflav	Soy Protein	N	Base value	Value	P within	P btw Soy	Value	P vs Control	Population	Applicability	Quality
Diet	Xover	Dairy															
Meinertz 2002	4.5 wk	ISP w/Isoflavones, liquid				2.39/g [b]	20%	1	83	*-21*	<0.001	NS [c]	*-6*	NS [c]	♀♂	↑	C
		ISP w/o Isoflavones, liquid				0.11/g [b]	20%	2	84	*-18*	<0.01		*-3*	NS [c]			
		Casein diet, liquid							79	*-15*	<0.01						
Meinertz 1989	4.5 wk	ISP diet, liquid cholesterol enriched					112	1 1	102	*-32*			-16	0.02 [c]	♀♂	↑	C
		Calcium caseinate								*-19*							
Meinertz 1988	4 wk	ISP diet, liquid low cholesterol					113	1 0	110	*-42*			*+1*	NS [c]	♀♂	↑	C
		Casein diet, liquid low cholesterol								*-43*							
Diet	Xover	Animal/Usual															
Wong 1998 [d]	5 wk	ISP diet					>15%	1	111	*-13*			*-8*	0.03	♂	↑	B
		Animal diet						3	109	*-5*							
Supplement	Xover	Dairy															
Steinberg 2003	6 wk	ISP w/Isoflavones	55	47	5	107	25	2	112	*-1*		NS	*-3*	NS	post♀	↑	C
		ISP w/o Isoflavones	1	0.5	0.5	2	24	4		*-1*			*-3*	NS			
		Total milk protein								*+2*							
Supplement	RCT	Dairy															
Murray 2003	26 wk	ISP + Estradiol 0.5 mg	66	44	10	120	38	8	120	*0*	NS		*+7*	NS	post♀	↑	C
		Total milk protein+ Estradiol 0.5 mg						7	125	*-7*	NS						
		ISP + Estradiol 1.0 mg	66	44	10	120	38	8	129	*-22*	NS		*-26*				
		Total milk protein + Estradiol 1.0 mg						7	164 [e]	*+4*	NS						
Supplement	Xover	Miscellaneous															
Washburn 1999	6 wk	ISP w/Isoflavones once daily				34	14	4	127	*-8*		nd	-9	<0.05 [c]	peri♀	↑	B
		ISP w/Isoflavones twice daily				34	14	2		*-10*			-9	<0.01 [c]			
		Carbohydrates								*-2*							
Onning 1998	4 wk	Soy milk					23/30 [f]	1	112	-8	<0.05		*-4*		♀♂	↑	B
		Oat milk						2		-4	NS						
Supplement	RCT	Miscellaneous															
Takatsuka 2000	9 wk	Soy milk				109	17	2 7	91	*-5*	NS		-8	NS	pre♀	↑	B
		No supplement						2 5	94	*+3*	NS						
Supplement	Xover	No Control															
Merz-Demlow 2000	13 wk	ISP w/Isoflavones	70	47	10	128	53	1 3	84 [g]	*-5*		<0.05	--		pre♀	↑	C
		ISP w/Isoflavones	35	24	5	64	53			*+2*		--	--				
		ISP w/o Isoflavones	5	4	1	10	53			*+4*		--	--				
		No control group						--									

Apparent discrepancies between Within-Cohort changes and Between-Cohort changes are due to rounding errors in estimated Within-Cohort changes compared to reported Between-Cohort changes.

[a] Or difference between final values, as noted.

[b] Per gram protein. No data on number of grams of protein.

[c] Difference of final values (cross-over study)

[d] Wong 1998: Sub-analyses of same study in LDL<130 and LDL>130 tables.

[e] Non-significantly higher at baseline than other study arms because of single outlier with hypertriglyceridemia.

[f] Women/Men

[g] Measurements made at 4 menstrual cycle phases: early follicular, midfollicular, periovulatory, midluteal. Data extracted for periovulatory only. LDL change was greatest during this phase in high isoflavone group.

Table 15. Summary of sub-group analyses of adjusted linear regressions for low density lipoprotein (LDL)

Association Sub-group of studies		No. of Studies [a]	Association Beta (95% CI)	P-value [b]
Baseline LDL v Net Change LDL				
All studies	All studies	**59**		**NS**
	LDL >130 mg/dL	45	-0.14 (-0.28, +0.00)	0.06
Isoflavone only	All studies	11		NS
	LDL >130 mg/dL	11		NS
Protein w/Isoflavones	All studies	42 [c]		NS [c]
	LDL >130 mg/dL	30	-0.10 (-0.23, +0.02)	0.09
Soy Isoflavone Dose v Net Change LDL				
All studies	All studies	**43**		**NS**
	LDL >130 mg/dL	34		NS
Isoflavone only	All studies	10		NS
	LDL >130 mg/dL	10		NS
Protein w/Isoflavones	All studies	27		NS
	LDL >130 mg/dL	20		NS
Soy Protein Dose v Net Change LDL [c]				
All studies	All studies	**52**	**-0.10 (-0.20, +0.01)**	**0.08**
	LDL >130 mg/dL	41	-0.14 (-0.27, -0.00)	0.04
	Dose >10 g/day	43		NS
Protein w/Isoflavones	All studies	38		NS
	LDL >130 mg/dL	28	-0.16 (-0.33, +0.02)	0.08
	Dose <80 g/day	35	-0.16 (-0.33, +0.02)	0.07

NS, non-significant; w/, with; w/o, without

[a] Studies with sufficient data for adjusted linear regression.

[b] All associations were non-significant in multivariate analysis with baseline LDL, isoflavone dose, and soy protein dose.

[c] With all 42 studies, beta = -0.07 (95% CI –0.13, -0.00), *P*=0.05; however, with the omission of a single study (Puska, 2004), which found a large net change (-15 mg/dL) with a high mean baseline (198 mg/dL), the association was non-significant (*P*=0.4)

Figure 3. Net change of low density lipoprotein (LDL) with soy product consumption compared to control, by baseline level, isoflavone content, and soy protein content. Studies without non-soy control are not included. Studies without data on isoflavone or protein content are omitted from relevant graphs. ISP w/Iso = soy protein with isoflavones; ISP w/o Iso = soy protein without isoflavones; suppl = supplement.
Dashed lines represent adjusted regressions for studies with sufficient data for regression. Regression lines are drawn only within the range of independent variable (x-axis) data examined. P-values and number of studies included in regressions are shown. Both regression lines drawn are for all studies with abnormal baseline LDL.

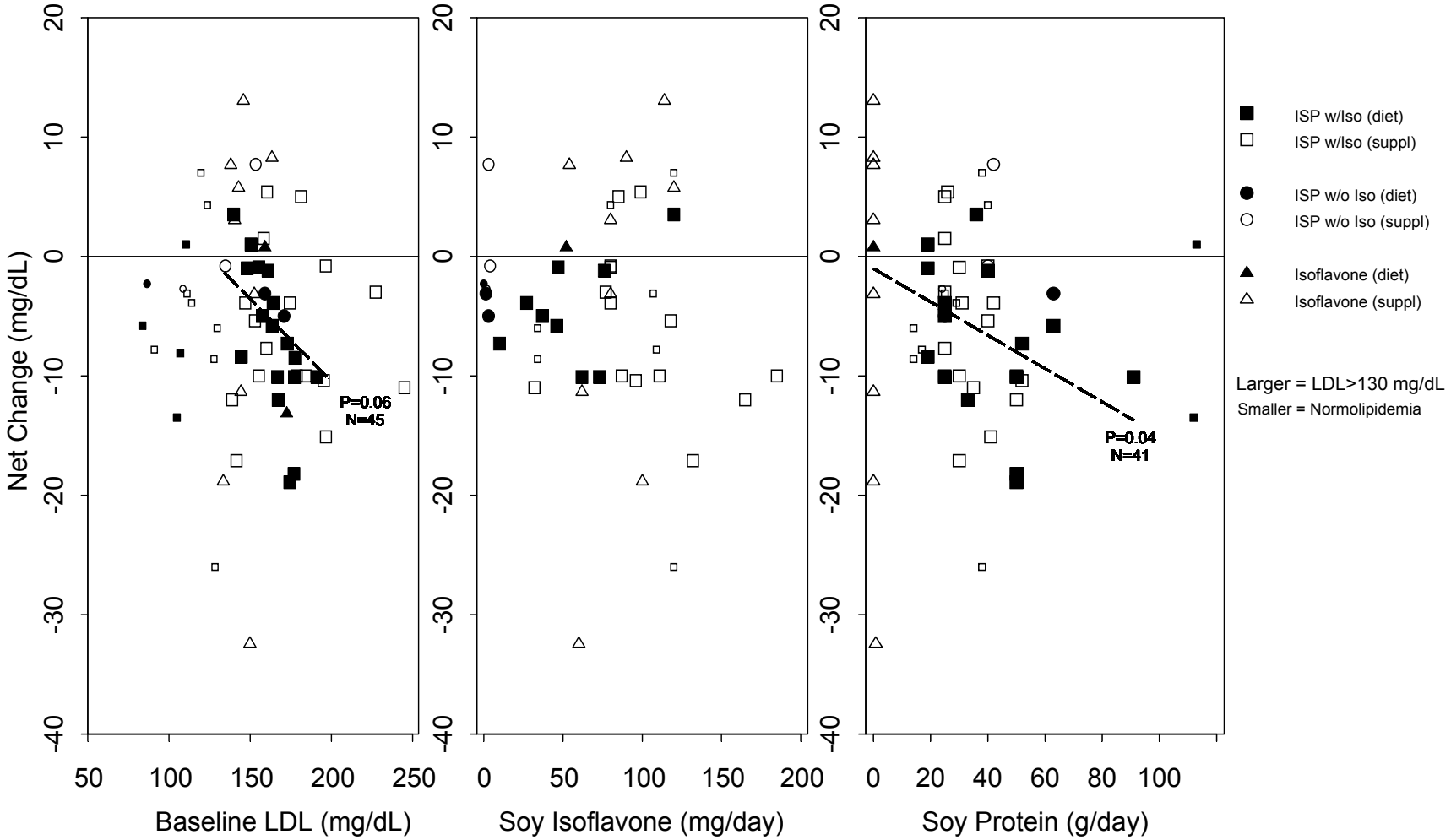


Figure 4. Meta-analysis of the effect of soy products on low density lipoprotein (LDL) in all randomized trials with non-soy controls. Circles represent net effect on LDL of individual study cohorts vs. non-soy controls; their size is proportional to the square root of the sample size. Black diamond represents summary mean net change using a random effects model meta-analysis. Bars (and values in parentheses) represent 95% confidence intervals. Cohorts are ordered from lowest (top) to highest mean baseline LDL. Sub-analyses of studies with normal and elevated baseline LDL (>130 mg/dL) are also shown (open diamonds). N indicates sample size of subjects consuming soy products.

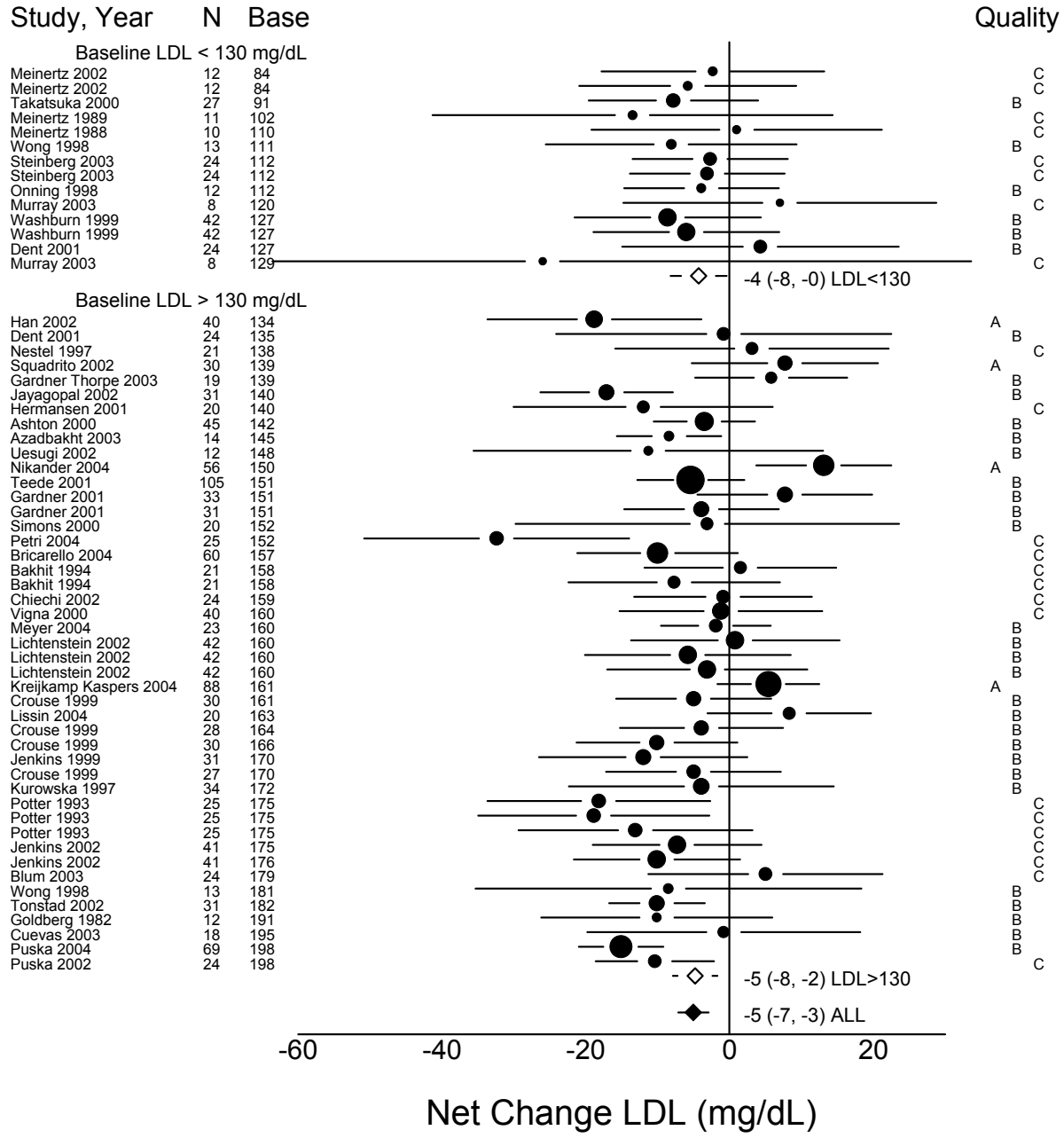
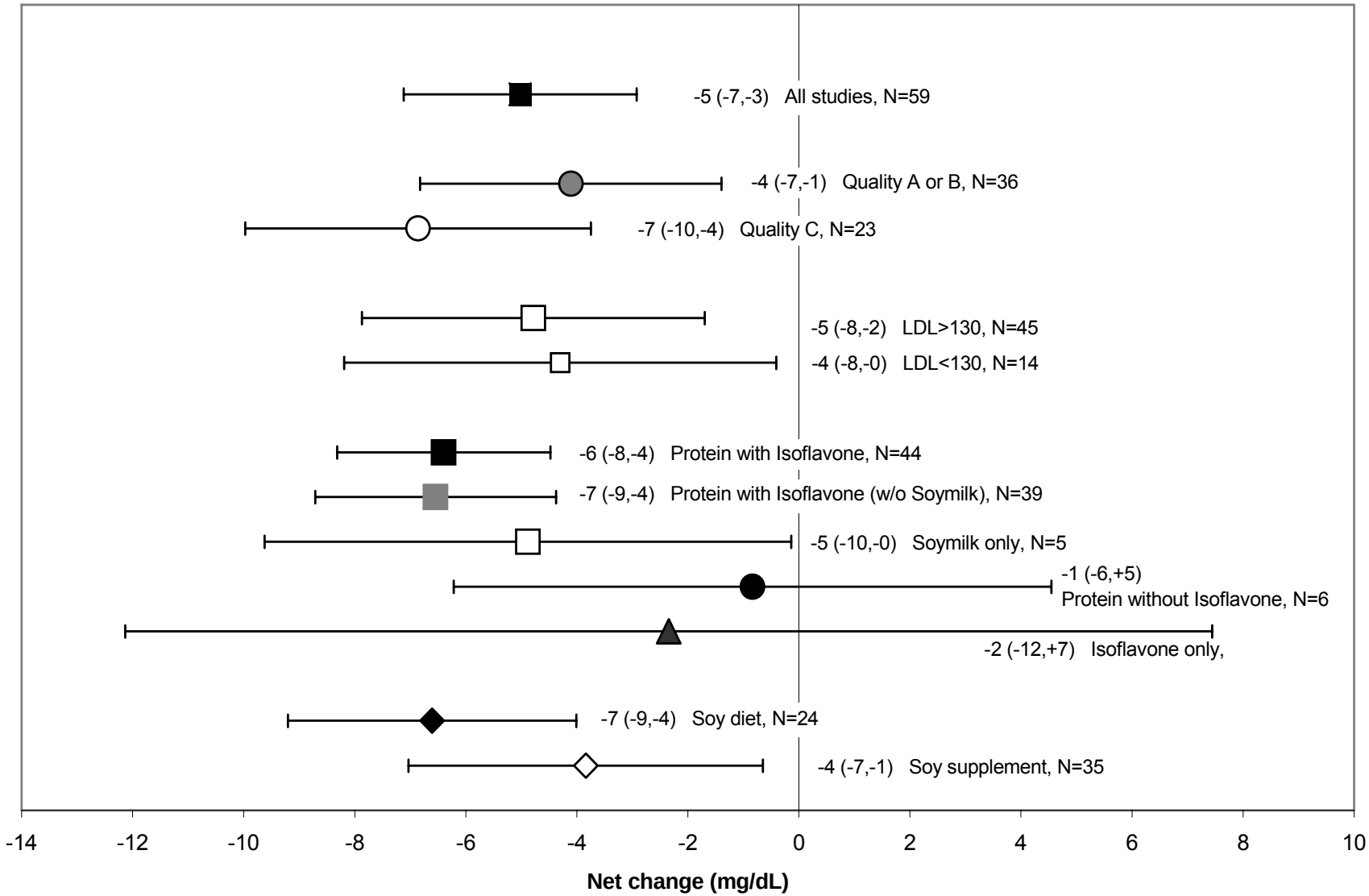


Figure 5. Meta-analysis summary estimates of net change low density lipoprotein (LDL) for different sub-analyses, as noted. Point estimate, 95% confidence interval, analysis group, and number of studies in each analysis group displayed.



3.2.4. Lipids: High Density Lipoprotein

(Tables 16-19, Figures 6-7)

Study Descriptions

We found 61 studies that reported on the effect of the consumption of soy products on high density lipoprotein (HDL). Of these, 5 reported only that there was no effect on HDL.[45-48,73] The remaining 56 studies are described below.[23,24,49-60,62-72,74,76-93,95-100,102-106]

For ease of categorization, we have divided the studies into separate tables as follows: 5 studies investigated soy products in subjects with abnormally low HDL (mean <40 mg/dL in men or <50 mg/dL in women, Table 16); 20 studies investigated dietary soy protein in subjects with normal HDL (Table 17); 23 studies investigated soy protein used as dietary supplements in subjects with normal HDL (Table 18); and 10 studies investigated pure soy isoflavones in subjects with normal HDL (Table 19). Some studies included cohorts of subjects in multiple categories.

The range of daily soy isoflavone intake among studies of soy products with isoflavones was approximately 10 to 185 mg, with a median of 80 mg per day. The range of daily soy protein intake among relevant studies was approximately 14 to 113 g, with a median of 39 g per day. Three of the 5 studies of subjects with, on average, abnormal HDL were restricted to men; 1 included both men and women; 1 included only pre-menopausal women. The large majority of studies had, on average, subjects with normal HDL. These studies mostly included post-menopausal women or both men and post-menopausal women. The large majority of studies were of limited applicability, even within the categories of pre- or post-menopausal women, or men. Only 12 of the studies were graded as being broadly applicable. Among the 56 studies, 5 were rated good quality (A), 29 were rated fair quality (B), and 20 were rated poor quality (C).

Overall Effect

Across the 56 studies there was a wide and evenly distributed range of effects of soy products on HDL. Approximately half of the cohorts of subjects consuming soy had a net increase in HDL compared to control, implying a benefit of soy; one-quarter found a net effect of 0 mg/dL, and one-quarter found a small net decrease in HDL. Across studies, net change ranged from –4 to +13 mg/dL, with the median net change equal to +1 mg/dL, and a fairly even distribution of net changes across the studies (Figure 6). Random effects model meta-analysis of non-soy-controlled studies with sufficient data (Figure 7) estimated a summary net change of +0.6 (95% CI –0.5, +1.8) mg/dL.

Soy Product, Dose, Other Variables

Analyses across studies

Figure 6 graphs the net change compared to non-soy control of all cohorts evaluated (that included a non-soy cohort). The left-most graph displays net change in HDL in relationship the baseline HDL level; this graph includes all studies. The middle graph compares net change to daily soy isoflavone consumption (among those studies that report isoflavone content). The right-most graph compares net change to daily soy protein consumption (among those studies that report soy protein content). Study cohorts who consumed soy with isoflavones are indicated by squares; cohorts who consumed soy without isoflavones are indicated by circles; and cohorts who consumed soy isoflavone without soy protein are indicated by triangles. Black symbols represent cohorts where the soy product was consumed as part of the regular diet; open symbols

represent cohorts where the soy product was consumed as a supplement to the diet (including soy milk products). Larger symbols indicate cohorts whose mean HDL was abnormally low at baseline; smaller symbols indicate cohorts with normal HDL at baseline.

Visual inspection of the graphs reveal no difference across studies in net effect on HDL based on baseline HDL levels, amount of soy isoflavones consumed, or amount of soy protein consumed. Likewise, there are no clear differences across studies based on whether the soy products were consumed as part of the diet (i.e., specifically replacing other sources of protein) or as a supplement (consumed in addition to regular diet). Also comparing the net effects of soy protein with isoflavones to soy protein without isoflavones to isoflavones without soy protein reveals similar ranges of effects for all 3 types of products.

Random effects model meta-regression across all studies yielded a statistically significant association between mean baseline HDL and net change HDL, such that each *increase* in baseline HDL of 1 mg/dL was associated with an additional net *increase* 0.12 (95% CI 0.07, 0.18) mg/dL HDL (P=0.00002). However, exclusion of the 2 studies with atypically small standard deviations (Kreijkamp-Kaspers 2004 and Onning 1998) yielded a non-significant association (P=0.6). Meta-regression of both isoflavone and soy protein dose revealed no association across studies with net change HDL.

Separate meta-analyses of those studies with normal and low baseline HDL (<40 mg/dL in men and/or <50 mg/dL in women) also suggested a larger net benefit of soy consumption among people with normal rather than low baseline HDL (Figure 7). However, again, the apparent differences in effect are largely driven by the 2 studies with atypically small standard deviations (Kreijkamp-Kaspers 2004 and Onning 1998). No difference in effect size was found comparing low quality studies (rated C) to studies of higher quality.

Effect of baseline level of abnormal lipids on net change HDL in individual studies

Two studies performed sub-analyses comparing the effect of soy products on HDL in subjects with different baseline levels of abnormal lipids. Both Crouse 1999[51] (Table 17) and Lichtenstein 2002[56] (Tables 17 and 19) found no overall difference in effect among subjects depending on lipidemia level, despite some significant effects or dose-effect trends in those with lower levels of LDL (LDL between 140 and 166 mg/dL, or LDL below 160 mg/dL, respectively).

Effect of soy isoflavone dose on net change HDL in individual studies

Fourteen studies[49,51,52,54,56,80-82,86-88,98,102,106] directly compared soy products with different levels of isoflavones, ranging from 0 mg/day to 185 mg/day. All reported no clinical difference in effect and, when reported, no statistically significant difference between isoflavone doses. In a single study by Crouse 1999[51] (Table 17), only among subjects with lower levels of abnormal lipids, was the relationship between soy isoflavone intake (ranging from 3 mg/day to 62 mg/day) and change in HDL statistically significant; though the individual treatments were each non-significant and the actual net effects were similar (0 to +4 mg/dL).

Effect of soy protein dose on net change HDL in individual studies

Four studies directly compared soy products with different amounts of soy protein.[50,52,56,80] The doses compared ranged from 0 g/day to 55 g/day in women and 71 g/day in men. Three of the studies, Teixera 2000[52] (Table 17), Tonstad 2002[80] (Table 18), and Potter 1993[50] (Table 16) reported no difference in effect related to soy protein dose. Lichtenstein 2002[56] (Tables 17 and 19) reported a significant, though small, difference in effect related to the

consumption of soy protein; however, those subjects who *did not* consume soy protein had an increase in HDL as opposed to those who did consume soy protein. Similar direction effects were seen among the majority of the other 3 studies.

Effect of soy as diet vs. supplement on net change HDL in individual studies

Only a single study directly compared consumption of soy product as a replacement of dietary protein to soy product as a supplement to usual diet. Verrillo 1985[67] (Tables 17 and 18) found an approximately 8 percent increase in HDL among subjects with severe hypercholesterolemia who consumed isolated soy protein replacing part of their diet compared to a similar *decrease* in HDL among those who supplemented their diets with isolated soy protein. It was not reported whether either of these changes were statistically significant or different from each other.

Effect of sex and menopausal status on net change HDL

Across studies, there was no clear difference in effect evident based on sex or menopausal status of the subjects. Four studies directly compared effects in different populations (data not included in summary tables). Crouse 1999[51] (Table 17) reported no difference in effect on HDL between post-menopausal women pre-menopausal women. Jenkins 2002[49] (Table 17) reported no significant difference in effect between men and women. Both Onning 1998[104] (Table 16) and Teede 2001[77] (Table 18) reported data suggesting no clinical difference in effect between men and women.

Summary

See Section 3.2.6.

Table 16. Effect of soy product on high density lipoprotein (mg/dL) in subjects with abnormal HDL (Baseline HDL<50 in women / <40 in men)

Diet/Supplement	Design	Control	Dose								Change			Net Change [a]				
			mg/day				g/day											
Author Year	Duration	Intervention	Genistein	Daidzein	Glycitein	T Isoflav	Soy Protein	N	Base value	Value	P within	P btw Soy	Value	P vs Control	Population	Applicability	Quality
Diet	Xover	Dairy															
Potter 1993	4 wk	ISP + cellulose					50	24	37	*-2*	NS	nd	*0*	NS [b]	♂	🧍	C
		ISP + cotyledon					50			*-2*	NS		*0*	NS [b]			
		Soy flour					0			*0*	NS		*+2*	NS [b]			
		Non-fat dry milk+ cellulose								*-2*	NS						
Diet	Xover	Animal/Usual															
Wong 1998 [c]	5 wk	ISP diet					>15%	13	39	*-2*			*+3*	NS	♂	🧍	B
		Animal diet							41	*-5*							
Supplement	Xover	Miscellaneous															
Gardner-Thorpe 2003	6 wk	Soy flour biscuits	45	75		120		19	39	*+4*			0	NS [b]	♂	🧍	B
		Wheat flour biscuits								*+4*							
Onning 1998	4 wk	Soy milk					23/30 [d]	12	42	0	NS		*0*		♀♂	🧍	B
		Oat milk								0	NS						
Supplement	Xover	No Control															
Merz-Demlow 2000	13 wk	ISP w/Isoflavones	70	47	10	128	53	13	48 [e]	*+1*		NS	--		pre♀	🧍	C
		ISP w/Isoflavones	35	24	5	64	53			*+1*			--				
		ISP w/o Isoflavones	5	4	1	10	53			*0*			--				
		No control group						--									

Apparent discrepancies between Within-Cohort changes and Between-Cohort changes are due to rounding errors in estimated Within-Cohort changes compared to reported Between-Cohort changes.

[a] Or difference between final values, as noted.
[b] Difference of final values (cross-over study)
[c] Wong 1998: Sub-analyses of same study in LDL<130 and LDL>130 tables.
[d] Women/Men
[e] Measurements made at 4 menstrual cycle phases: early follicular, midfollicular, periovulatory, midluteal. Data extracted for periovulatory only. LDL change was greatest during this phase in high isoflavone group.

Table 17. Effect of soy product diets on high density lipoprotein (mg/dL) in subjects with normal HDL (Baseline HDL>50 in women / >40 in men)

Diet/Supplement	Design	Control	Dose							Change			Net Change [a]				
			mg/day				g/day										
Author Year	Duration	Intervention	Genistein	Daidizein	Glycitein	T Isoflav	Soy Protein	N	Base value	Value	P within	P btw Soy	Value	P vs Control	Population	Applicability	Quality
Diet	Xover	Dairy															
Jenkins 2002 12145008	4 wk	ISP w/Isoflavones				73	50	41	51	*-3*		NS	*+1*	<0.01	post♀ ♂	👫	C
		ISP w/Isoflavones				10	52		51	*-2*			*+2*	<0.05			
		Low fat dairy+egg protein							51	*-4*							
Meinertz 2002	4.5 wk	ISP w/Isoflavones, liquid				2.39/g [b]	20%	12	61	*-7*	NS	NS [c]	*+3*	<0.05 [c]	♀♂	🧍	C
		ISP w/o Isoflavones, liquid				0.11/g [b]	20%		60	*-8*	NS		*+2*	NS [c]			
		Casein diet, liquid							59	*-10*	<0.05						
Meinertz 1989	4.5 wk	ISP diet, liquid cholesterol enriched					112	11	58	*-2*			+9	<0.01 [c]	♀♂	🧍	C
		Calcium caseinate								*-10*							
Meinertz 1988	4 wk	ISP diet, liquid low cholesterol					113	10	47	*0*			*+1*	NS [c]	♀♂	🧍	C
		Casein diet, liquid low cholesterol								*-1*							
Diet	RCT	Dairy															
Crouse 1999	9 wk	ISP w/Isoflavones				62	25	30	46	*+1*		NS	*+2*	NS	♀♂ (LDL 140-200)	👫	B
		ISP w/Isoflavones				37	25	30	45	*+1*			*+2*	NS			
		ISP w/Isoflavones				27	25	27	45	*0*			*+1*	NS			
		ISP w/o Isoflavones				3	25	28	47	*-1*			*0*	NS			
		Casein						31	45	*-1*							
		ISP w/Isoflavones				62	25	15	46	*-1*		NS	*+1*	NS	♀♂ LDL 166-200		
		ISP w/Isoflavones				37	25	12	48	*-2*			*0*	NS			
		ISP w/Isoflavones				27	25	15	45	*+2*			*+4*	NS			
		ISP w/o Isoflavones				3	25	12	45	*-2*			*0*	NS			
		Casein						16	48	*-2*							
		ISP w/Isoflavones				62	25	15	47	*+2*		<0.04 Trend	*+2*	NS	♀♂ LDL 140-166		
		ISP w/Isoflavones				37	25	18	42	*+4*			*+4*	NS			
		ISP w/Isoflavones				27	25	12	44	*0*			*0*	NS			
		ISP w/o Isoflavones				3	25	16	48	*0*			*0*	NS			
		Casein						15	41	*0*							
Teixeira 2000	6 wk	ISP w/Isoflavones				95	50	15	44	*+1*		nd	*+1*	NS	♂	👫👫	A
		ISP w/Isoflavones				76	40	17	43	*+2*			*+2*	NS			
		ISP w/Isoflavones				57	30	18	44	*+2*			*+2*	NS			
		ISP w/Isoflavones				38	20	15	41	*+1*			*+1*	NS			
		Calcium caseinate						16	42	*0*	NS						

continued

Table 17. Continued

Diet/Supplement	Design	Control	Dose							Change			Net Change [a]				
			mg/day				g/day										
Author Year	Duration	Intervention	Genistein	Daidizein	Glycitein	T Isoflav	Soy Protein	N	Base value	Value	P within	P btw Soy	Value	P vs Control	Population	Applicability	Quality
Diet	RCT	Dairy															
Baum 1998	24 wk	ISP w/Isoflavones	35	23	6	90	40	21	53	*+2*		nd	+4	<0.03	post♀	↑	B
		ISP w/o Isoflavones	2	1	2	56	40	23	52	+3			+5	<0.01			
		Casein + non-fat dry milk						22	53	*-2*							
Vigna 2000	12 wk	ISP w/Isoflavones				76	40	40	61	*0*	NS		*+1*		post♀	↑	C
		Caseinate						37	62	*-1*	NS						
Van Horn 2001	6 wk	ISP w/Isoflavones + oats	39	19			19	32	61	0	NS		*+1*		post♀	↑	B
		Milk + oats						32	67	-1	NS						
		ISP w/Isoflavones + wheat	39	19			19	31	64	0	NS		*+1*				
		Milk + wheat						32	63	-1	NS						
Diet	Xover	Animal/Usual															
Lichtenstein 2002 [d]	6 wk	ISP w/Isoflavones	27	14	5	46	55/71 [e]	42	51	*0*		NS	*-2*	Soy: 0.03 Iso: NS [c]	post♀ ♂		
		ISP w/o Isoflavones	0.4	0.8	0	1.3	55/71 [e]			*0*			*-2*				
		Animal w/Isoflavones [d]	27	21	4	52	0			*+2*			*0*				
		Animal w/o Isoflavones								*+2*							
		ISP w/Isoflavones	27	14	5	46	55/71 [e]	22	nd	55 [f]		nd	*-1*[c]	Soy: NS Iso: NS [c]	post♀ ♂ LDL>160	↑	B
		ISP w/o Isoflavones	0.4	0.8	0	1.3	55/71 [e]			56 [f]			*0*[c]				
		Animal w/Isoflavones [d]	27	21	4	52	0			53 [f]			*-3*[c]				
		Animal w/o Isoflavones								56 [f]							
		ISP w/Isoflavones	27	14	5	46	55/71 [e]	20	nd	49 [f]		nd	*+2*[c]	Soy: 0.04 Iso: NS [c]	post♀ ♂ LDL<160		
		ISP w/o Isoflavones	0.4	0.8	0	1.3	55/71 [e]			49 [f]			*+2*[c]				
		Animal w/Isoflavones [d]	27	21	4	52	0			48 [f]			*+1*[c]				
		Animal w/o Isoflavones								47 [f]							
Ashton 2000 11194529	4 wk	ISP diet	84	35		120	36	42	48	*0*			-3	0.01 [c]	♂	↑	C
		Lean meat diet								*+3*							
Azadbakht 2003	7 wk	ISP diet					19	14	47	+3	<0.05		+2	NS	♀♂ DM Proteinuria	↑	B
		Usual diet							46	+1	NS						
Wong 1998 [g]	5 wk	ISP diet					>15%	13	41	*-3*			*0*	NS	♂	↑	B
		Animal diet							41	*-3*							
Goldberg 1982	6 wk	ISP diet					91	12	45	*-1*	NS		*-1*	NS [c]	♀♂	↑	B
		Animal diet								*0*	NS						
Diet	RCT	Animal/Usual															
Chiechi 2002 11836040	26 wk	ISP diet[h]				47		58/24 [j]	52	-2	NS		*+2*		post♀	↑	C
		Usual diet[h]						55/43 [j]	55	-4	<0.05						
Shorey 1981	6 wk	ISP diet					55	13	52	-8	0.001		*-4*		♂	↑	C
		Animal diet						11	46	-4	NS						
Diet	Xover	Miscellaneous															
Jenkins 1999	4 wk	ISP diet					33	31	49	*-3*			*0*	NS	post♀ ♂	↑	B
		Vegetarian diet							48	*-3*							
Diet	RCT	Miscellaneous															
Murkies 1995	12 wk	Soy flour	40 g of flour per day					23	67	*-2*	NS		*0*	NS	post♀	↑	B
		Wheat flour						24	63	*-2*	NS						
Sagara 2004	5 wk	Soy powder baked goods				80	20	25	54	+4	<0.01		*-1*	0.06	♂	↑	B
		Usual baked goods						25	55	+5	<0.01						

continued

Table 17. Continued.

Author Year	Duration	Intervention	Dose mg/day Genistein	Daidizein	Glycitein	T Isoflav	Dose g/day Soy Protein	N	Base value	Change Value	Change P within	Change P btw Soy	Net Change [a] Value	Net Change [a] P vs Control	Population	Applicability	Quality
Diet	**RCT**	**No Control**															
Verrillo 1985 [k]	16 wk	ISP, supplement [k]					31	38	54	-4		nd	--		♀♂	👪	B
		ISP, 60 g replacing dietary protein					31	19	50	+4			--				
		No control group						--									

Apparent discrepancies between Within-Cohort changes and Between-Cohort changes are due to rounding errors in estimated Within-Cohort changes compared to reported Between-Cohort changes.

[a] Or difference between final values, as noted.
[b] Per gram protein. No data on number of grams of protein.
[c] Difference of final values (cross-over study)
[d] Lichtenstein: In both Isoflavone and ISP tables.
[e] Women/Men
[f] Final values. No data on baseline or change from baseline.
[g] Wong 1998: Sub-analyses of same study in LDL<130 and LDL>130 tables.
[h] No data on how fat content of 2 diets compare.
[j] N: baseline/final.
[k] Verrillo: In both diet and supplement tables.

Table 18. Effect of soy product supplements on high density lipoprotein (mg/dL) in subjects with normal HDL (Baseline HDL>50 in women / >40 in men)

Author Year	Duration	Intervention	Dose mg/day Genistein	Daidizein	Glycitein	T Isoflav	Dose g/day Soy Protein	N	Base value	Change Value	Change P within	Change P btw Soy	Net Change [a] Value	Net Change [a] P vs Control	Population	Applicability	Quality
Supplement	**Xover**	**Dairy**															
Bricarello 2004	6 wk	Soy milk[b]	50	33	5	87	25	60	58	*+4*	<0.05		*+5*	<0.05	♀♂	👪	C
		Non-fat milk[b]								*-1*							
Kurowska 1997	4 wk	Soy milk					31	34	51	*+3*			*+3*	0.04	♀♂	👪	B
		Milk, 2% fat								*0*							
Blum 2003 12659466	6 wk	ISP w/Isoflavones				85	25	24	60	*-1*	NS		*-3*	NS [d]	post♀	🧍	C
		Total milk protein								*+2*							
Steinberg 2003	6 wk	ISP w/Isoflavones	55	47	5	107	25	24	60	*-2*		NS	*-4*	NS	post♀	🧍	C
		ISP w/o Isoflavones	1	0.5	0.5	2	24			*0*			*-2*	NS			
		Total milk protein								*+2*							
Meyer 2004	5 wk	Soy milk/yogurt				80	30	23	49	*+3*			+2	NS [d]	post♀ ♂	🧍	B
		Low fat milk/yogurt								*0*							
Bakhit 1994	4 wk	ISP + cellulose					25	21	51	*-1*	NS		*0*	NS [c]	♂	🧍	C
		ISP + cotyledon					25			*-1*	NS		*+1*				
		Casein + cellulose								*-1*	NS						
		Casein + cotyledon								*-2*	NS						
		ISP + cellulose					25	11	53	*-3*	NS		*-3*	NS [c]	♂ TC>220		
		ISP + cotyledon					25			*-3*	NS		*0*				
		Casein + cellulose								*0*	NS						
		Casein + cotyledon								*-3*	NS						
Hermansen 2001	6 wk	ISP w/Isoflavones				>165	50	20	51	*+3*			*+1*	NS	♀♂ DM	🧍	C
		Casein							49	*+2*							

continued

Table 18. Continued.

Diet/Supplement / Author Year	Design / Duration	Control / Intervention	Dose mg/day Genistein	Daidizein	Glycitein	T Isoflav	g/day Soy Protein	N	Change Base value	Value	P within	P btw Soy	Net Change [a] Value	P vs Control	Population	Applicability	Quality
Supplement	Xover	Dairy															
Cuevas 2003	8 wk	ISP w/Isoflavones	48	24	8	80	<40	18	54	*-1*	NS		*+2*	NS [d]	post ♀	↑	B
		Caseinate								*-3*	<0.05						
Supplement	RCT	Dairy															
Teede 2001	13 wk	ISP w/Isoflavones	77	38	5	118	40	86	56	-2	NS		*+2*	NS	post ♀♂	↑	B
		Casein						93	58	-4	<0.05						
Kreijkamp-Kaspers 2004	52 wk	ISP w/Isoflavones	52	41	6		26	88[e]	59	*0*			+2	0.09	post ♀	↑	A
		Total milk protein						87[e]	59	*-2*							
Puska 2004	8 wk	ISP w/Isoflavones				153	41	69	64	+2			0	NS	post ♀♂	↑	B
		Yogurt						74	66	+2							
Gardner 2001	12 wk	ISP w/Isoflavones	52	25	4	80	42	31	58	*+4*		NS	*+4*	NS	post ♀	↑	B
		ISP w/o Isoflavones	2	1	0	3	42	33	54	*+4*			*+4*	NS			
		Milk protein						30	58	*0*							
Tonstad 2002	16 wk	ISP w/Isoflavones				185	50	31	52	*+5*		nd	+2	NS	post ♀♂	↑	B
		ISP w/Isoflavones				111	30	34	57	*+3*							
		Casein, 50 g						29	51	*0*							
		Casein 30 g						36	49	*+3*							
Dent 2001	24 wk	ISP w/Isoflavones				80	40	24	58 [f, g]	*-5 [g]*		NS	*-3 [g]*	NS	peri♀	↑	B
		ISP w/o Isoflavones				4	40	24	56 [f, g]	*-1 [g]*			*+1 [g]*				
		Whey protein						21	57 [f, g]	*-2 [g]*							
Puska 2002	6 wk	ISP w/Isoflavones				96	52	24	61	+3			0	NS	post ♀♂	↑	C
		Calcium caseinate						28	60	+3							
Murray 2003	26 wk	ISP + Estradiol 0.5 mg	66	44	10	120	38	8	64	*+4*	NS		*0*	NS	post ♀	↑	C
		Total millk protein + Estradiol 0.5 mg						7	67	*+4*	NS						
		ISP + Estradiol 1.0 mg	66	44	10	120	38	8	69	*-5*	NS		*+3*				
		Total millk protein + Estradiol 1.0 mg						7	62	*-2*	NS						
Supplement	Xover	Miscellaneous															
Washburn 1999	6 wk	ISP w/Isoflavones once daily				34	14	42	55	*-3*		nd	-1	NS [d]	peri♀	↑	B
		ISP w/Isoflavones twice daily				34	14			*-3*			-1	NS [d]			
		Carbohydrates								*-2*							
Jayagopal 2002	12 wk	ISP w/Isoflavones	70	49	13	132	30	31	51	+0.4	NS		*0*	NS	post ♀ DM	↑	B
		Cellulose							50	+0.6	NS						
Supplement	RCT	Miscellaneous															
Takatsuka 2000	9 wk	Soy milk				109	17	27	66	*-2*	NS		-4		pre♀	↑	B
		No supplement						25	63	*+2*	NS						
Supplement	Xover	No Control															
Wangen 2001	13 wk	ISP w/Isoflavones	70	47	10	128	53	18	52	*+1*	NS	NS [d]	--		post ♀	↑	C
		ISP w/Isoflavones	35	24	5	64	53	18/17 [h]		*+1*	NS		--				
		ISP w/o Isoflavones	5	4	1	10	53	18		*0*	NS		--				
		No control group						--									

continued

Table 18. Continued.

Diet/Supplement	Design	Control	Dose						Change			Net Change [a]				
			mg/day				g/day									
Author Year	Duration	Intervention	Genistein	Daidzein	Glycitein	T Isoflav	Soy Protein	N	Base value	Value	P within	P btw Soy	Value	P vs Control	Population	Applicability	Quality
Supplement	RCT	No Control															
Gallagher 2004	39 wk	ISP w/Isoflavones	52	28		96	40	17	53	*-2*	<0.05	nd	--		post♀	👪	C
		ISP w/Isoflavones	28	20		52	40	19	52	-5	<0.05		--				
		ISP w/o Isoflavones	4	0		4	40	14	52	*-4*	<0.05		--				
		No control group						--									
Mackey 2000 Female study	12 wk	ISP w/Isoflavones				65	28	25	59	*0*	NS	NS	--		post♀	👪	B
		ISP w/o Isoflavones				4	28	24	64	*+2*			--				
		No control group						--									
Verrillo 1985 [j]	16 wk	ISP, supplement					31	38	54	-4		nd	--		♀♂	👪	B
		ISP, 60 g replacing dietary protein [j]					31	19	50	+4			--				
		No control group						--									

Apparent discrepancies between Within-Cohort changes and Between-Cohort changes are due to rounding errors in estimated Within-Cohort changes compared to reported Between-Cohort changes.

[a] Or difference between final values, as noted.
[b] Unequal amounts of fat in soy milk (17.5 g/day) and cow milk (0 g/day).
[c] Main effect of soy protein
[d] Difference of final values (cross-over study)
[e] Intention-to-treat analysis (75 completed soy protocol, 78 completed control protocol)
[f] Graph
[g] Median value, difference or net difference of median values.
[h] N: baseline/final.
[j] Verrillo: In both diet and supplement tables.

Table 19. Effect of soy isoflavones (without soy protein) on high density lipoprotein (mg/dL)

Diet/Supplement	Design	Control	Dose							Change			Net Change [a]				
			mg/day				g/day										
Author Year	Duration	Intervention	Genistein	Daidizein	Glycitein	T Isoflav	Soy Protein	N	Base value	Value	P within	P btw Soy	Value	P vs Control	Population	Applicability	Quality
Baseline HDL > 50 (Women) / 40 (Men)																	
Diet	Xover	Animal/Usual															
Lichtenstein 2002 [b]	6 wk	ISP w/Isoflavones [b]	27	14	5	46	55/71 [c]	42	51	*0*		NS	*-2*	Soy: 0.03 Iso: NS [d]	post♀ ♂		
		ISP w/o Isoflavones [b]	0.4	0.8	0	1.3	55/71 [c]			*0*			*-2*				
		Animal w/Isoflavones	27	21	4	52	0			*+2*			*0*				
		Animal w/o Isoflavones								*+2*							
		ISP w/Isoflavones [b]	27	14	5	46	55/71 [c]	22	nd	55[e]		nd	*-1*[d]	Soy: NS Iso: NS [d]	post♀ ♂ LDL>160		B
		ISP w/o Isoflavones [b]	0.4	0.8	0	1.3	55/71 [c]			56[e]			*0*[d]				
		Animal w/Isoflavones	27	21	4	52	0			53[e]			*-3*[d]				
		Animal w/o Isoflavones								56[e]							
		ISP w/Isoflavones [b]	27	14	5	46	55/71 [c]	20	nd	49[e]		nd	*+2*[d]	Soy: 0.04 Iso: NS [d]	post♀ ♂ LDL<160		
		ISP w/o Isoflavones [b]	0.4	0.8	0	1.3	55/71 [c]			49[e]			*+2*[d]				
		Animal w/Isoflavones	27	21	4	52	0			48[e]			*+1*[d]				
		Animal w/o Isoflavones								47[e]							
Supplement	Xover	Placebo															
Nikander 2004 15240647	13 wk	Isoflavones	6	42	66		0	56	69	-1	NS		*-1*		post♀ Breast CA		A
		Placebo							68	0	NS						
Nestel 1997	5 wk	Isoflavones	45	35	3	80	0	21	50	*-3*	NS		*-3*		post♀		C
		Placebo								*0*	NS						
Simons 2000	8 wk	Isoflavones				80	0	20	55	*-3*			*0*	NS [d]	post♀		B
		Placebo								*-3*							
Supplement	RCT	Placebo															
Uesugi 2002	4 wk	Isoflavones	0	0	0	62 [f]	0	12	66	*-1*	NS		*-4*	NS	peri♀		B
		Placebo						11	65	*+3*	NS						
Uesugi 2003	13 wk	Isoflavones	0	0	0	62 [f]	0	11	65	*-1*			*-1*	NS	post♀		B
		Dextrin						10	71	*0*							
Baseline HDL < 50 (Women) / 40 (Men)																	
Supplement	RCT	Placebo															
Han 2002	13 wk	Isoflavones	70	19	11	100	0	40	40	*+4*	<0.05		*0*	NS	post♀		A
		Placebo						40	40	*+4*	<0.05						
Squadrito 2002	26 wk	Genistein	54				0	30	46	*0*	NS		*-4*	NS	post♀		A
		Placebo						30	46	*+4*	NS						
Petri 2004	26 wk	Soy germ capsules				60	0.8	25	44 [g]	*+13*	<0.05		*+13*		post♀		B
		Lactose capsules						25	48 [g]	*0*	NS						
Dewell 2002	9 wk	Isoflavones	40	50		90	0	20	46	*-8*			*0*	NS	post♀		C
		Placebo						16	46	*-8*							

Apparent discrepancies between Within-Cohort changes and Between-Cohort changes are due to rounding errors in estimated Within-Cohort changes compared to reported Between-Cohort changes.

[a] Or difference between final values, as noted.
[b] Lichtenstein: In both Isoflavone and ISP tables.
[c] Women/Men
[d] Difference of final values (cross-over study)
[e] Final values. No data on baseline or change from baseline.
[f] 31 mg daidzin, 7 mg genistin, 21 mg glycitin
[g] Graph

Figure 6. Net change of high density lipoprotein (HDL) with soy product consumption compared to control, by baseline level, isoflavone content, and soy protein content. Studies without non-soy control are not included. Studies without data on isoflavone or protein content are omitted from relevant graphs. ISP w/Iso = soy protein with isoflavones; ISP w/o Iso = soy protein without isoflavones; suppl = supplement.

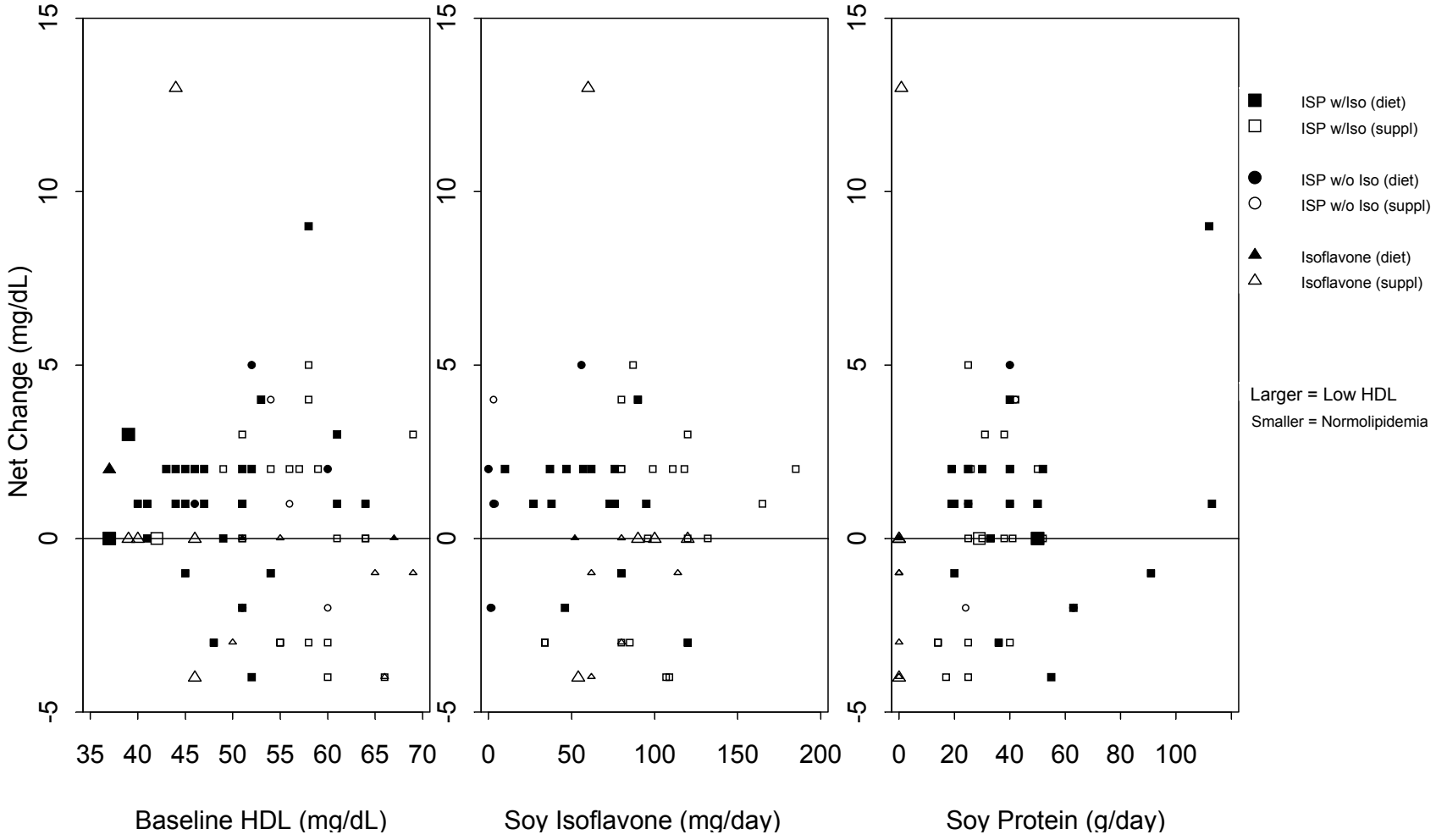
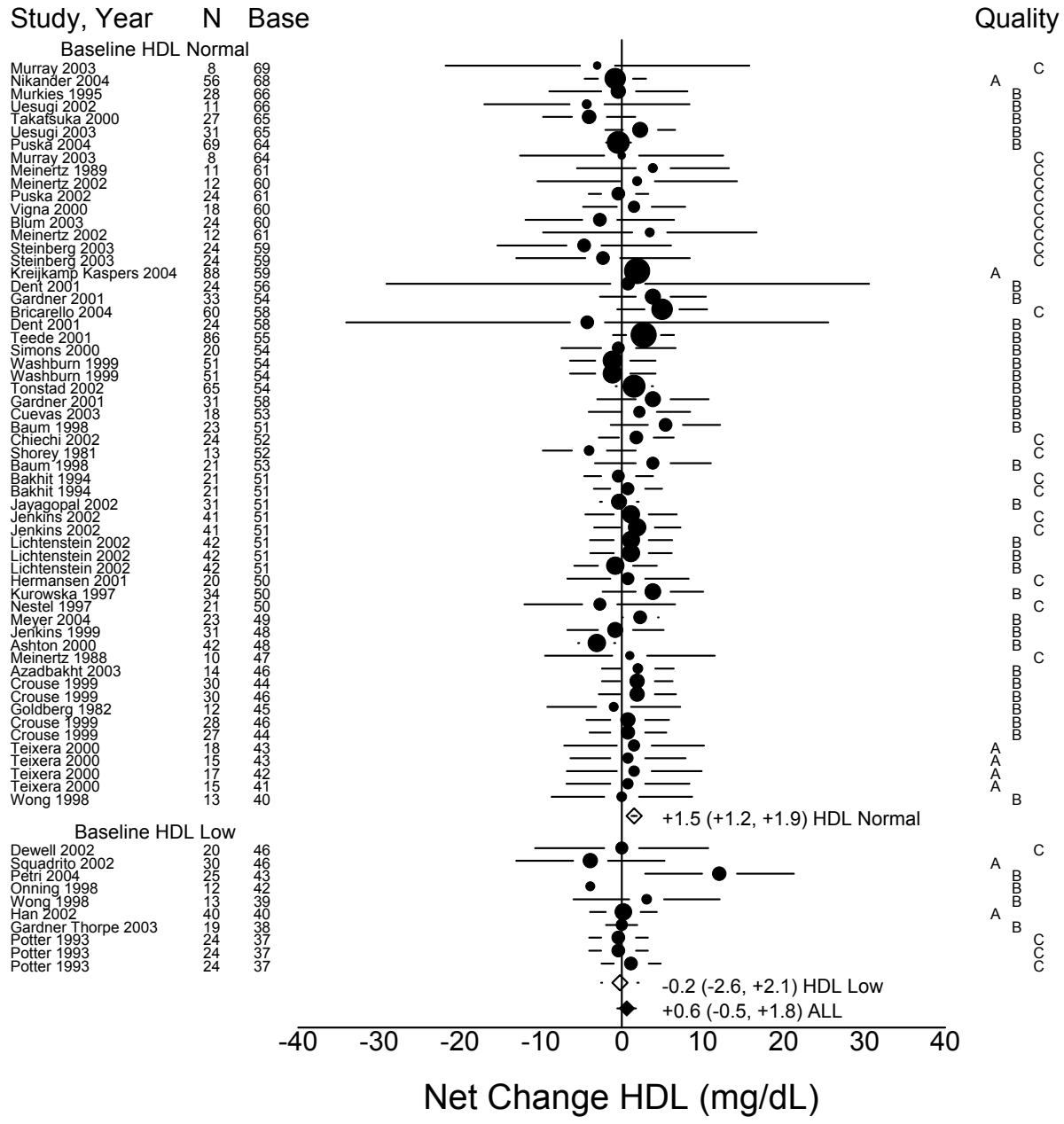


Figure 7. Meta-analysis of the effect of soy products on high density lipoprotein (HDL) in all randomized trials with non-soy controls. Circles represent net effect on HDL of individual study cohorts vs. non-soy controls; their size is proportional to the square root of the sample size. Black diamond represents summary mean net change using a random effects model meta-analysis. Bars (and values in parentheses) represent 95% confidence intervals. Cohorts are ordered from lowest (top) to highest mean baseline HDL. Sub-analyses of studies with normal and low baseline HDL (<50 (women) / <40 (men) mg/dL) are also shown (open diamonds). N indicates sample size of subjects consuming soy products.



3.2.5. Lipids: Triglycerides

(Tables 20-24, Figures 8-9)

Study Descriptions

We found 57 studies that reported on the effect of the consumption of soy products on triglycerides. Of these, 3 reported only that there was no effect on triglycerides.[46,47,73] The remaining 54 studies are described below.[23,24,49-52,54-60,62-64,66-72,74,76-93,95-100,102-106]

For ease of categorization, we have divided the studies into separate tables as follows: 10 studies investigated dietary soy protein in subjects with hypertriglyceridemia (mean triglycerides >150 mg/dL, Table 20); 7 studies investigated soy protein supplements in subjects with hypertriglyceridemia (Table 21); 10 studies investigated pure soy isoflavones (Table 22); 10 studies investigated dietary soy protein in subjects with normal triglyceride levels (Table 23); and 19 studies investigated soy protein supplements in subjects with normal triglyceride levels (Table 24). Some studies included cohorts of subjects in multiple categories.

The range of daily soy isoflavone intake among studies of soy products with isoflavones was approximately 10 to 185 mg, with a median of 80 mg per day. The range of daily soy protein intake among relevant studies was approximately 14 to 113 g, with a median of 38 g per day. Sixteen studies included subjects with, on average, abnormal triglycerides; the remainder included, on average, subjects with normal triglycerides. The large majority of studies were of limited applicability, even within the categories of pre- or post-menopausal women, or men. Only 12 of the studies were graded as being broadly applicable. Among the 54 studies, 5 were rated good quality (A), 27 were rated fair quality (B), and 22 were rated poor quality (C).

Overall Effect

Across the 54 studies there was a widely distributed range of effects of soy products on triglycerides (Figure 8). Approximately two-thirds of the cohorts of subjects consuming soy had a net decrease in triglycerides compared to control, implying a benefit of soy. Across studies, net change ranged from –49 to +66 mg/dL, with the median net change equal to –3 mg/dL. In terms of percent net change (using the baseline level in the soy intervention cohort as the denominator), net change ranged from approximately –49% to +31%, with a median net change equal to –2%. Random effects model meta-analysis of non-soy-controlled studies with sufficient data (Figure 9) resulted in a statistically significant net change estimate of –8 (95% CI –11, –5) mg/dL.

Soy Product, Dose, Other Variables

Analyses across studies

Figure 8 graphs the net change compared to non-soy control of all cohorts evaluated (that included a non-soy cohort). The left-most graph displays net change in triglycerides in relationship the baseline triglycerides level; this graph includes all studies. The middle graph compares net change to daily soy isoflavone consumption (among those studies that report isoflavone content). The right-most graph compares net change to daily soy protein consumption (among those studies that report soy protein content). Study cohorts who consumed soy with isoflavones are indicated by squares; cohorts who consumed soy without isoflavones are indicated by circles; and cohorts who consumed soy isoflavone without soy protein are indicated by triangles. Black symbols represent cohorts where the soy product was consumed as part of the regular diet; open symbols represent cohorts where the soy product was consumed as a supplement to the diet (including soy milk products). Larger symbols indicate cohorts whose

mean triglycerides was abnormally low at baseline; smaller symbols indicate cohorts with normal triglycerides at baseline.

Visual inspection of the graphs reveal a possible negative association between baseline triglycerides levels and net change triglycerides across studies (net reductions are larger at higher baseline triglycerides. However, net reductions in triglyceride appear to be greater at both low doses of soy isoflavones and low doses of soy proteins. Similar patterns appear for all 3 types of products.

Separate meta-analyses of studies based on elevated (>150 mg/dL) or normal baseline triglycerides revealed a modest difference in effect between the 2 groups of studies, although both meta-analyses were statistically significant (Figure 9). Among studies with elevated baseline triglycerides, the net reduction with soy consumption was greater (–11 [95% CI –16, –7]) than among studies with normal baseline triglycerides (–5 [95% CI –9, 0]). Sub-analysis of poor quality studies (rated C) revealed no significant difference in effect compared to better quality studies.

Random effects model meta-regression across all studies found a similar effect, such that for each increase in mean baseline triglycerides of 10 mg/dL, the additional net change in triglycerides with soy consumption was –0.8 mg/dL (95% CI –0.13, –0.02). There was no clear threshold baseline level where there was a substantial, consistent change in the association between baseline triglycerides and net change triglycerides. By meta-regression, neither isoflavone or soy protein dose was associated with net effect on triglycerides.

Effect of baseline level of abnormal lipids on net change triglycerides in individual studies

Three studies performed sub-analyses comparing the effect of soy products on triglycerides in subjects with different baseline levels of abnormal lipids. Both Bakhit 1994[72] (Table 21) and Lichtenstein 2002[56] (Tables 22 and 23) found no overall difference in effect among subjects depending on lipid levels (thresholds of total cholesterol at 220 mg/dL or LDL at 160 mg/dL, respectively). Crouse 1999[51] (Table 20) did report larger, statistically significant reductions among those with more elevated LDL (>166 mg/dL).

Effect of soy isoflavone dose on net change triglycerides in individual studies

Fourteen studies[49,51,52,54,56,80-82,86-88,98,102,106] directly compared soy products with different levels of isoflavones, ranging from 0 mg/day to 185 mg/day. Only 1 study reported a significantly different effect based on isoflavone dose. Consistent with the apparent association across studies, Meinertz 2002[98] (Table 23) found a significantly larger reduction in triglycerides when subjects were consuming liquid isolated soy protein with minimal isoflavones than when they consumed equivalent soy protein with isoflavones.

Effect of soy protein dose on net change triglycerides in individual studies

Four studies directly compared soy products with different amounts of soy protein.[50,52,56,80] The doses compared ranged from 0 g/day to 55 g/day in women and 71 g/day in men. Three of the studies, Teixera 2000[52] (Table 20), Tonstad 2002[80] (Table 24), and Potter 1993[50] (Table 20) reported no difference in effect related to soy protein dose. Lichtenstein 2002[56] (Tables 22 and 23) reported a highly significant difference in effect related to the consumption of soy protein, where a larger net reduction was seen among subjects when they consumed soy products with soy protein than soy isoflavones alone.

Effect of soy as diet vs. supplement on net change triglycerides in individual studies

Only a single study directly compared consumption of soy product as a replacement of dietary protein to soy product as a supplement to usual diet. Verrillo 1985[67] (Tables 20 and 21 found no difference in effect on triglycerides whether soy was consumed as a dietary replacement or as a supplement.

Effect of sex and menopausal status on net change triglycerides

Across studies, there was no clear difference in effect evident based on sex or menopausal status of the subjects. Four studies directly compared effects in different populations (data not included in summary tables). Crouse 1999[51] (Table 20) reported no difference in effect on triglycerides between post-menopausal women pre-menopausal women. Jenkins 2002[49] (Table 20) reported no significant difference in effect between men and women. Both Onning 1998[104] (Table 24) and Teede 2001[77] (Table 24) reported data suggesting no clinical difference in effect between men and women.

Summary

See Section 3.2.6.

Table 20. Effect of soy product diets on triglycerides (mg/dL) in subjects with abnormal Tg (Baseline Tg>150 mg/dL)

Diet/Supplement	Design	Control	Dose							Change			Net Change [a]				
			mg/day				g/day										
Author Year	Duration	Intervention	Genistein	Daidzein	Glycitein	T Isoflav	Soy Protein	N	Base value	Value	P within	P btw Soy	Value	P vs Control	Population	Applicability	Quality
Diet	Xover	Dairy															
Jenkins 2002 12145008	4 wk	ISP w/Isoflavones				73	50	41	173	*+7*	NS	NS	*-3*	NS	post♀ ♂	↑	C
		ISP w/Isoflavones				10	52		163	*-12*			*-22*	NS			
		Low fat dairy+egg protein							173	*+10*							
Potter 1993	4 wk	ISP + cellulose					50	23	173	*+4*	NS	nd	*-26*	NS [b]	♂	↑	C
		ISP + cotyledon					50			*+4*	NS		*-26*	NS [b]			
		Soy flour					0			*+15*	NS		*-15*	NS [b]			
		Non-fat dry milk + cellulose								*+30*	NS						
Diet	RCT	Dairy															
Crouse 1999	9 wk	ISP w/Isoflavones				62	25	30	153	*0*		NS	*-14*	NS	♀♂ (LDL 140-200)	↑	B
		ISP w/Isoflavones				37	25	30	150	*-5*			*-19*	NS			
		ISP w/Isoflavones				27	25	27	166	*-12*			*-26*	NS			
		ISP w/o Isoflavones				3	25	28	144	*+8*			*-6*	NS			
		Casein						31	153	*+14*							
		ISP w/Isoflavones				62	25	15	146	*-7*		NS	*-37*	<0.03	♀♂ LDL 166-200		
		ISP w/Isoflavones				37	25	12	147	*-2*			*-32*	NS			
		ISP w/Isoflavones				27	25	12	162	*-16*			*-46*	<0.03			
		ISP w/o Isoflavones				3	25	15	156	*+15*			*-15*	NS			
		Casein						16	141	*+30*							
		ISP w/Isoflavones				62	25	15	161	*+5*		NS	*+8*	NS	♀♂ LDL 140-166		
		ISP w/Isoflavones				37	25	18	151	*-7*			*-4*	NS			
		ISP w/Isoflavones				27	25	12	171	*-13*			*-10*	NS			
		ISP w/o Isoflavones				3	25	16	136	*+2*			*+5*	NS			
		Casein						15	166	*-3*							

continued

Table 20. Continued.

Diet/Supplement	Design	Control	Dose					N	Base value	Change			Net Change [a]		Population	Applicability	Quality
			mg/day				g/day										
Author Year	Duration	Intervention	Genistein	Daidizein	Glycitein	T Isoflav	Soy Protein			Value	P within	P btw Soy	Value	P vs Control			
Diet	**RCT**	**Dairy**															
Teixeira 2000	6 wk	ISP w/Isoflavones				95	50	15	193	*+32*		nd	+16	NS	♂	👥	A
		ISP w/Isoflavones				76	40	17	181	*+7*			-9	NS			
		ISP w/Isoflavones				57	30	18	223	*-22*			-38	NS			
		ISP w/Isoflavones				38	20	15	157	*+14*			-2	NS			
		Calcium caseinate						16	189	*+16*	NS						
Baum 1998	24 wk	ISP w/Isoflavones	35	23	6	90	40	21	154	*0*		nd	*-1*	NS	post♀	👥	B
		ISP w/o Isoflavones	2	1	2	56	40	23	167	*-14*			*-15*	NS			
		Casein+non-fat dry milk						22	155	*+1*							
Diet	**Xover**	**Animal/Usual**															
Ashton 2000 11194529	4 wk	ISP diet	84	35		120	36	42	173	*-30*			-13	0.02 [b,c]	♂	👥	C
		Lean meat diet								*-17*							
Azadbakht 2003	7 wk	ISP diet					19	14	243	-10	<0.05		-13	<0.002	♀♂ DM Proteinuria	🧍	B
		Usual diet							241	+3	<0.05						
Wong 1998 [d]	5 wk	ISP diet					>15%	13	210	*+56*			*+66*	NS	♂	🧍	B
		Animal diet							260	*-10*							
Diet	**Xover**	**Miscellaneous**															
Jenkins 1999	4 wk	ISP diet					33	31	158	*-11*			*-25*	0.07	post♀♂	👥	B
		Vegetarian diet							158	*+14*							
Diet	**RCT**	**No Control**															
Verrillo 1985 [e]	16 wk	ISP, supplement [e]					31	38	195	-35		NS	--		♀♂	👥	B
		ISP, 60 g replacing dietary protein					31	19	150	-18			--				
		No control group						--									

Apparent discrepancies between Within-Cohort changes and Between-Cohort changes are due to rounding errors in estimated Within-Cohort changes compared to reported Between-Cohort changes.

[a] Or difference between final values, as noted.
[b] Difference of final values (cross-over study)
[c] However 95% confidence interval of net change crosses 0.
[d] Wong 1998: Sub-analyses of same study in LDL<130 and LDL>130 tables.
[e] Verrillo: In both diet and supplement tables.

Table 21. Effect of soy product supplements on triglycerides (mg/dL) in subjects with abnormal Tg (Baseline Tg>150 mg/dL)

Diet/Supplement	Design	Control	Dose								Change			Net Change [a]				
			mg/day				g/day											
Author Year	Duration	Intervention	Genistein	Daidzein	Glycitein	T Isoflav	Soy Protein	N	Base value	Value	P within	P btw Soy	Value	P vs Control	Population	Applicability	Quality
Supplement	Xover	Dairy															
Kurowska 1997	4 wk	Soy milk					31	34	155	*+17*			*+8*	NS	♀♂	↑	B
		Milk, 2% fat								*+9*							
Bakhit 1994	4 wk	ISP + cellulose					25	21	152	*-21*	NS		*-8*	NS [b]	♂	↑	C
		ISP + cotyledon					25			*-4*	NS		*+9*				
		Casein + cellulose								*-13*	NS						
		Casein + cotyledon								*-13*	NS						
		ISP + cellulose					25	11	175	*-49*	<0.05		*-20*	NS [b]	♂ TC>220		
		ISP + cotyledon					25			*-16*	NS		*+5*				
		Casein + cellulose								*-29*	NS						
		Casein + cotyledon								*-21*	NS						
Hermansen 2001	6 wk	ISP w/Isoflavones				>165	50	20	150	*-6*			*+14*	0.04 [c]	♀♂ DM	↑	C
		Casein							150	*+8*							
Cuevas 2003	8 wk	ISP w/Isoflavones	48	24	8	80	<40	18	190	*-55*	<0.05		*-25*	NS [d]	post♀	↑	B
		Caseinate								*-30*	NS						
Supplement	RCT	Dairy															
Puska 2002	6 wk	ISP w/Isoflavones				96	52	21	156	-12			+5	NS	post♀ ♂	↑	C
		Calcium caseinate						28	160	-17							
Supplement	Xover	Miscellaneous															
Jayagopal 2002	12 wk	ISP w/Isoflavones	70	49	13	132	30	32	195	-3	NS		*-8*	NS	post♀ DM	↑	B
		Cellulose							193	+5	NS						
Supplement	RCT	No Control															
Verrillo 1985 [e]	16 wk	ISP, supplement					31	38	195	-35		NS	--		♀♂	↑	B
		ISP, 60 g replacing dietary protein [e]					31	19	150	-18			--				
		No control group						--									

Apparent discrepancies between Within-Cohort changes and Between-Cohort changes are due to rounding errors in estimated Within-Cohort changes compared to reported Between-Cohort changes.

[a] Or difference between final values, as noted.
[b] Main effect of soy protein
[c] NS for difference between final values.
[d] Difference of final values (cross-over study)
[e] Verrillo: In both diet and supplement tables.

Table 22. Effect of soy isoflavones (without soy protein) on triglycerides (mg/dL)

Author Year	Duration	Intervention	Dose mg/day Genistein	Daidzein	Glycitein	T Isoflav	Dose g/day Soy Protein	N	Base value	Change Value	Change P within	Change P btw Soy	Net Change [a] Value	Net Change [a] P vs Control	Population	Applicability	Quality
Tg <150 mg/dL																	
Diet	Xover	Animal/Usual															
Lichtenstein 2002 [b]	6 wk	ISP w/Isoflavones [b]	27	14	5	46	55/71 [c]	42	136 [d]	*-24*		<0.05	*-15*	Soy: <0.0001 Iso: NS [e]	post♀ ♂	↑	B
		ISP w/o Isoflavones [b]	0.4	0.8	0	1.3	55/71 [c]			*-24*			*-15*				
		Animal w/Isoflavones	27	21	4	52	0			*-7*			*+2*				
		Animal w/o Isoflavones								*-9*							
		ISP w/Isoflavones [b]	27	14	5	46	55/71 [c]	22	nd	119 [d,f]		nd	*-8* [e]	Soy: <0.0001 Iso: NS [e]	post♀ ♂ LDL>160		
		ISP w/o Isoflavones [b]	0.4	0.8	0	1.3	55/71 [c]			110 [d,f]			*-17* [e]				
		Animal w/Isoflavones	27	21	4	52	0			126 [d,f]			*-1* [e]				
		Animal w/o Isoflavones								127 [d,f]							
		ISP w/Isoflavones [b]	27	14	5	46	55/71 [c]	20	nd	107 [d,f]		nd	*-21* [e]	Soy: 0.01 Iso: NS [e]	post♀ ♂ LDL<160		
		ISP w/o Isoflavones [b]	0.4	0.8	0	1.3	55/71 [c]			114 [d,f]			*-14* [e]				
		Animal w/Isoflavones	27	21	4	52	0			132 [d,f]			*+4* [e]				
		Animal w/o Isoflavones								128 [d,f]							
Supplement	Xover	Placebo															
Nikander 2004 15240647	13 wk	Isoflavones	6	42	66		0	56	108	+1	NS		*+1*		post♀ Breast CA	↑	A
		Placebo							111	0	NS						
Nestel 1997	5 wk	Isoflavones	45	35	3	80	0	21	128	+7	NS		*+20*		post♀	↑	C
		Placebo								*-13*	NS						
Simons 2000	8 wk	Isoflavones				80	0	20	99	*0*			*+4*	NS [e]	post♀	↑	B
		Placebo								*-4*							
Supplement	RCT	Placebo															
Squadrito 2002	26 wk	Genistein	54				0	30	133	*+27*	NS		*+36*	NS	post♀	↑	A
		Placebo						30	150	*-9*	NS						
Petri 2004	26 wk	Soy germ capsules				60	0.8	25	150 [g]	*0*	NS		*-4*		post♀	↑	B
		Lactose capsules						25	139 [g]	*+4*	NS						
Dewell 2002	26 wk	Isoflavones	40		50	90	0	20/17 [h]	71	+9			*0*	NS	post♀	↑	C
		Placebo						16	115	+9							
Uesugi 2002	4 wk	Isoflavones	0	0	0	62 [j]	0	12	95	*+11*	NS		*+19*	NS	peri♀	↑	B
		Placebo						11	105	*-8*	NS						
Uesugi 2003	13 wk	Isoflavones	0	0	0	62 [j]	0	11	127	*-14*			*-32*	NS	post♀	↑	B
		Dextrin						10	118	*+18*							
Tg >=150 mg/dL																	
Supplement	RCT	Placebo															
Han 2002	13 wk	Isoflavones	70	19	11	100	0	40	204	+7	<0.05		*-3*	NS	post♀	↑	A
		Placebo						40	176	*+10*	<0.05						

Apparent discrepancies between Within-Cohort changes and Between-Cohort changes are due to rounding errors in estimated Within-Cohort changes compared to reported Between-Cohort changes.

[a] Or difference between final values, as noted.
[b] Lichtenstein: In both Isoflavone and ISP tables.
[c] Women/Men
[d] Values log-transformed prior to statistical analysis.
[e] Difference of final values (cross-over study)
[f] Final values. No data on baseline or change from baseline.
[g] Graph
[h] N: baseline/final.
[j] 31 mg daidzin, 7 mg genistin, 21 mg glycitin

Table 23. Effect of soy product diets on triglycerides (mg/dL) in subjects with normal Tg (Baseline Tg<150 mg/dL)

Diet/Supplement	Design	Control	Dose							Change			Net Change [a]				
			mg/day				g/day										
Author Year	Duration	Intervention	Genistein	Daidizein	Glycitein	T Isoflav	Soy Protein	N	Base value	Value	P within	P btw Soy	Value	P vs Control	Population	Applicability	Quality
Diet	Xover	Dairy															
Meinertz 2002	4.5 wk	ISP w/Isoflavones, liquid				2.39/g[b]	20%	12	88	*-15*	NS	<0.05 [c]	*-3*	NS [c]	♀♂	↑	C
		ISP w/o Isoflavones, liquid				0.11/g [b]	20%		81	*-23*	<0.01		*-11*	NS [c]			
		Casein diet, liquid							77	*-12*	NS						
Meinertz 1989	4.5 wk	ISP diet, liquid cholesterol enriched					112	11	58	*-4*			+1	NS [c]	♀♂	↑	C
		Calcium caseinate								*-5*							
Meinertz 1988	4 wk	ISP diet, liquid low cholesterol					113	10	68	*-5*			*+7*	NS [c]	♀♂	↑	C
		Casein diet, liquid low cholesterol								*-12*							
Diet	RCT	Dairy															
Vigna 2000	12 wk	ISP w/Isoflavones				76	40	40	130	*-14*	NS		*-2*		post♀	↑	C
		Caseinate						37	117	*-12*	NS						
Diet	Xover	Animal/Usual															
Lichtenstein 2002 [d]	6 wk	ISP w/Isoflavones	27	14	5	46	55/71 [e]	42	136 [f]	*-24*		<0.05	*-15*	Soy: <0.0001 Iso: NS [c]	post♀♂		
		ISP w/o Isoflavones	0.4	0.8	0	1.3	55/71 [e]			*-24*			*-15*				
		Animal w/Isoflavones [d]	27	21	4	52	0			*-7*			*+2*				
		Animal w/o Isoflavones								*-9*							
		ISP w/Isoflavones	27	14	5	46	55/71 [e]	22	nd	119 [f,g]		nd	*-8[c]*	Soy: <0.0001 Iso: NS [e]	post♀♂ LDL>160	↑	B
		ISP w/o Isoflavones	0.4	0.8	0	1.3	55/71 [e]			110 [f,g]			*-17[c]*				
		Animal w/Isoflavones [d]	27	21	4	52	0			126 [f,g]			*-1[c]*				
		Animal w/o Isoflavones								127 [f,g]							
		ISP w/Isoflavones	27	14	5	46	55/71 [e]	20	nd	107 [f,g]		nd	*-21[c]*	Soy: 0.01 Iso: NS [e]	post♀♂ LDL<160		
		ISP w/o Isoflavones	0.4	0.8	0	1.3	55/71 [e]			114 [f,g]			*-14[c]*				
		Animal w/Isoflavones [d]	27	21	4	52	0			132 [f,g]			*+4[c]*				
		Animal w/o Isoflavones								128 [f,g]							
Wong 1998 [h]	5 wk	ISP diet					>15%	13	89	*+9*			*+16*	NS	♂	↑	B
		Animal diet							92	*-7*							
Goldberg 1982	6 wk	ISP diet					91	12	116	*-12*	NS		*+1*	NS [c]	♀♂	↑	B
		Animal diet								*-13*	<0.05						
Diet	RCT	Animal/Usual															
Chiechi 2002 11836040	26 wk	ISP diet[j]				47		58/24 [k]	120	-3	NS		*-7*		post♀	↑	C
		Usual diet[j]						55/43 [k]	100	+4	NS						
Shorey 1981	6 wk	ISP diet					55	13	97	+40	0.046		*+28*		♂	↑	C
		Animal diet						11	130	+12	NS						
Diet	RCT	Miscellaneous															
Murkies 1995	12 wk	Soy flour						23	95	*-2*	NS		*-6*	NS	post♀	↑	B
		Wheat flour						24	96	*+4*	NS						

Apparent discrepancies between Within-Cohort changes and Between-Cohort changes are due to rounding errors in estimated Within-Cohort changes compared to reported Between-Cohort changes.

[a] Or difference between final values, as noted.
[b] Per gram protein. No data on number of grams of protein.
[c] Difference of final values (cross-over study)
[d] Lichtenstein: In both Isoflavone and ISP tables.
[e] Women/Men
[f] Values log-transformed prior to statistical analysis.
[g] Final values. No data on baseline or change from baseline.
[h] Wong 1998: Sub-analyses of same study in LDL<130 and LDL>130 tables.
[j] No data on how fat content of 2 diets compare.
[k] N: baseline/final.

Table 24. Effect of soy product supplements on triglycerides (mg/dL) in subjects with normal Tg (Baseline Tg<150 mg/dL)

Diet/Supplement	Design	Control	Dose							Change			Net Change [a]				
Author Year	Duration	Intervention	mg/day Genistein	mg/day Daidzein	mg/day Glycitein	mg/day T Isoflav	g/day Soy Protein	N	Base value	Value	P within	P btw Soy	Value	P vs Control	Population	Applicability	Quality
Supplement	Xover	Dairy															
Bricarello 2004	6 wk	Soy milk[b]	50	33	5	87	25	60	136	*-3*	NS		*+2*	NS	♀♂	↑	C
		Non-fat milk[b]								*-1*	NS						
Blum 2003 12659466	6 wk	ISP w/Isoflavones				85	25	24	133	*+60*	0.04		*-2*	NS [c]	post♀	↑	C
		Total milk protein								*+62*							
Steinberg 2003	6 wk	ISP w/Isoflavones	55	47	5	107	25	24	91	*+1*		NS	*+5*	NS	post♀	↑	C
		ISP w/o Isoflavones	1	0.5	0.5	2	24			*+4*			*+8*	NS			
		Total milk protein								*-4*							
Meyer 2004	5 wk	Soy milk/yogurt				80	30	23	115	*-7*			*-2*	NS [c]	post♀♂	↑	B
		Low fat milk/yogurt								*-4*							
Supplement	RCT	Dairy															
Teede 2001	13 wk	ISP w/Isoflavones	77	38	5	118	40	86	106	-17	<0.05		*-16*	NS	post♀♂	↑	B
		Casein						93	106	-1	NS						
Kreijkamp-Kaspers 2004	52 wk	ISP w/Isoflavones	52	41	6		26	88[d]	120	*+2*			-8	NS	post♀	↑	A
		Total milk protein						87[d]	111	*+10*							
Puska 2004	8 wk	ISP w/Isoflavones				153	41	69	149	+9			0	NS	post♀♂	↑	B
		Yogurt						74	148	+9							
Tonstad 2002	16 wk	ISP w/Isoflavones				185	50	31	118	*-18*		nd	-2	NS	post♀♂	↑	B
		ISP w/Isoflavones				111	50	34	113	*-14*							
		Casein, 50 g						29	129	*-9*							
		Casein 30 g						36	139	*-15*							
Gardner 2001	12 wk	ISP w/Isoflavones	52	25	4	80	42	31	115	*0*		NS	-9	NS	post♀♂	↑	B
		ISP w/o Isoflavones	2	1	0	3	42	33	115	*0*			-9	NS			
		Milk protein						30	115	*+9*							
Dent 2001	24 wk	ISP w/Isoflavones				80	40	24	94[e,f]	*+11*[f]		NS	*-33*[f]	NS	peri♀	↑↑↑	B
		ISP w/o Isoflavones				4	40	24	99[e,f]	*-5*[f]			*-49*[f]				
		Whey protein						21	72[e,f]	*+44*[f]							
Murray 2003	26 wk	ISP + Estradiol 0.5 mg	66	44	10	120	38	8	116	*+3*	NS		*+15*		post♀	↑	C
		Total millk protein+ Estradiol 0.5 mg						7	99	*-12*	NS						
		ISP + Estradiol 1.0 mg	66	44	10	120	38	8	97	*+53*	0.02		*-14*				
		Total millk protein + Estradiol 1.0 mg						7	191 [g]	*+67*	NS						

continued

Table 24. Continued.

Diet/Supplement Author Year	Design Duration	Control Intervention	Dose mg/day Genistein	Daidizein	Glycitein	T Isoflav	g/day Soy Protein	N	Base value	Change Value	P within	P btw Soy	Net Change [a] Value	P vs Control	Population	Applicability	Quality
Supplement	Xover	Miscellaneous															
Washburn 1999	6 wk	ISP w/Isoflavones once daily				34	14	42	131	*-3*		nd	-28	NS [c]	peri♀	↑	B
		ISP w/Isoflavones twice daily				34	14			*+10*			-15	NS [c]			
		Carbohydrates								*+25*							
Onning 1998	4 wk	Soy milk					23/30 [h]	12	80	+9	NS		*0*		♀♂	↑	B
		Oat milk								+9	NS						
Gardner-Thorpe 2003	6 wk	Soy flour biscuits	45	75		120		19	106	*+27*			0	NS [c]	♂	↑	B
		Wheat flour biscuits								*+27*							
Supplement	RCT	Miscellaneous															
Takatsuka 2000	9 wk	Soy milk				109	17	27	98	*-17*	NS		-1	NS	pre♀	↑	B
		No supplement						25	96	*-16*	NS						
Supplement	Xover	No Control															
Wangen 2001	13 wk	ISP w/Isoflavones	70	47	10	128	53	18	130	*-22*	NS	NS [c]	--		post♀	↑	C
		ISP w/Isoflavones	35	24	5	64	53	18/17 [j]		*-22*	NS		--				
		ISP w/o Isoflavones	5	4	1	10	53	18		*-27*	NS		--				
		No control group						--									
Merz-Demlow 2000	13 wk	ISP w/Isoflavones	70	47	10	128	53	13	56 [k]	*-4*		NS	--		pre♀	↑	C
		ISP w/Isoflavones	35	24	5	64	53			*-2*			--				
		ISP w/o Isoflavones	5	4	1	10	53			*+7*			--				
		No control group						--									
Supplement	RCT	No Control															
Gallagher 2004	39 wk	ISP w/Isoflavones	52	28		96	40	17	138	*+10*	NS	nd	--		post♀	↑	C
		ISP w/Isoflavones	28	20		52	40	19	135	*+6*	NS		--				
		ISP w/o Isoflavones	4	0		4	40	14	110	*+24*	NS		--				
		No control group						--									
Mackey 2000 Female study	12 wk	ISP w/Isoflavones				65	28	25	135	*+1*	NS	NS	--		post♀	↑	B
		ISP w/o Isoflavones				4	28	24	136	-7			--				
		No control group						--									

Apparent discrepancies between Within-Cohort changes and Between-Cohort changes are due to rounding errors in estimated Within-Cohort changes compared to reported Between-Cohort changes.

[a] Or difference between final values, as noted.
[b] Unequal amounts of fat in soy milk (17.5 g/day) and cow milk (0 g/day).
[c] Difference of final values (cross-over study)
[d] Intention-to-treat analysis (75 completed soy protocol, 78 completed control protocol)
[e] Graph
[f] Median value, difference or net difference of median values.
[g] Significantly higher at baseline than other study arms because of single outlier with hypertriglyceridemia.
[h] Women/Men
[j] N: baseline/final.
[k] Measurements made at 4 menstrual cycle phases: early follicular, midfollicular, periovulatory, midluteal. Data extracted for periovulatory only. LDL change was greatest during this phase in high isoflavone group.

Figure 8. Net change of triglycerides (Tg) with soy product consumption compared to control, by baseline level, isoflavone content, and soy protein content. Studies without non-soy control are not included. Studies without data on isoflavone or protein content are omitted from relevant graphs. ISP w/Iso = soy protein with isoflavones; ISP w/o Iso = soy protein without isoflavones; suppl = supplement.

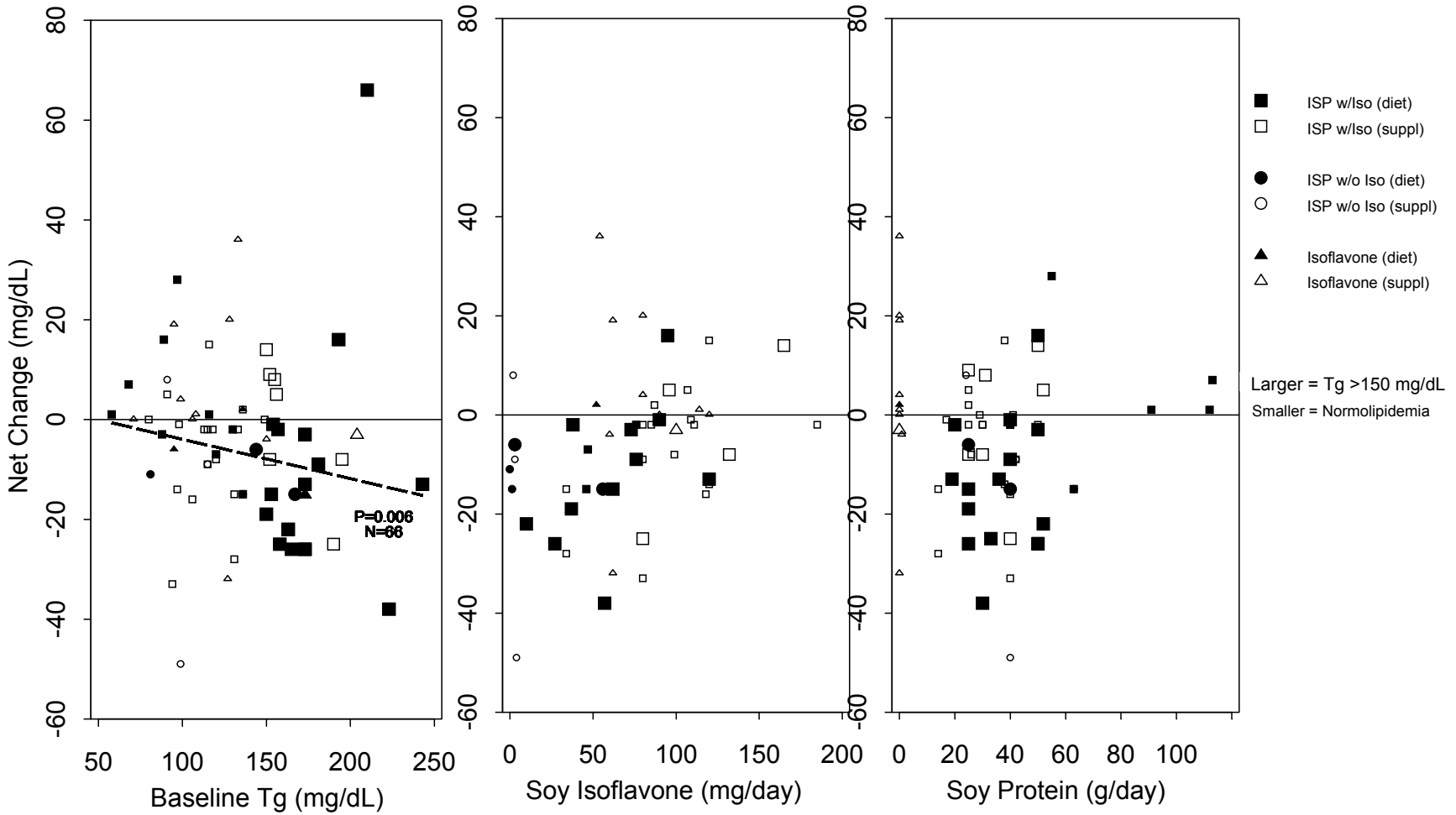
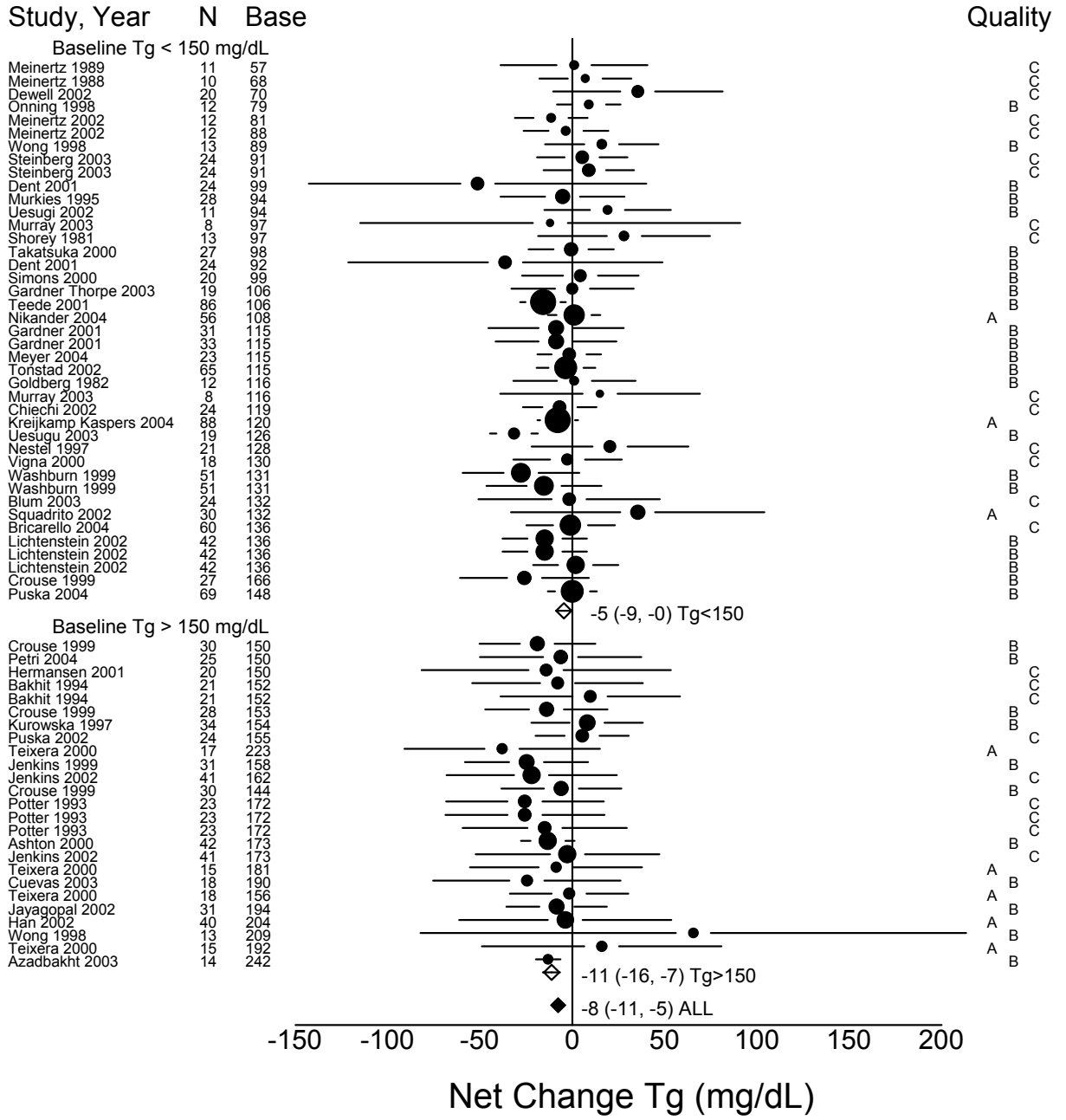


Figure 9. Meta-analysis of the effect of soy products on triglycerides in all randomized trials with non-soy controls. Circles represent net effect on triglycerides of individual study cohorts vs. non-soy controls; their size is proportional to the square root of the sample size. Black diamond represents summary mean net change using a random effects model meta-analysis. Bars (and values in parentheses) represent 95% confidence intervals. Confidence intervals of several studies are truncated. Cohorts are ordered from lowest (top) to highest mean baseline triglyceride level. Sub-analyses of studies with normal and elevated baseline triglycerides (>150 mg/dL) are also shown (open diamonds). N indicates sample size of subjects consuming soy products.



3.2.6. Summary of Lipid Profile Studies

(Tables 25-28)

Characteristics of the 68 randomized studies that reported data on total cholesterol, LDL, HDL, and/or triglycerides are summarized in Tables 25-28. Approximately three-quarters of the treatments evaluated were soy protein with isoflavones; the remaining treatments evaluated were about evenly divided between soy protein without isoflavones and isoflavones alone (without soy protein). Among studies with soy protein, the range of soy protein consumed daily was 14 to 113 g, with a median of 36 g per day. Among studies with soy isoflavones, the range of isoflavones consumed daily was 10 to 185 mg, with a median of 80 mg per day. These ranges were the same for all lipid profile studies. Few studies directly compared soy products, mostly comparing soy protein with varying amounts of soy isoflavones. Only one study, Lichtenstein 2002[56] performed a factorial design study comparing both present and absent soy protein and present and absent soy isoflavones, thus allowing analysis of both the effect of soy protein and soy product.

Total Cholesterol

A total of 61 studies reported data on the effect of consumption of soy products on total cholesterol levels. The median net change compared to control found was approximately –6 mg/dL (or –2.5%) with a wide range of effects, from –33 to +7 mg/dL (–12% to +4%). Across studies, there were no discernable differences in effect based on baseline total cholesterol, soy protein consumption, soy isoflavone consumption, soy incorporated into diet or as supplement, or population (post-menopausal women, pre-menopausal women, men). However, 2 studies reported greater net effect of soy in subjects with more severely elevated lipids. Most studies that directly compared different doses of soy protein or soy isoflavones found no significant difference in effect, although results were mixed. Most studies that also directly compared effect in men and women found no difference.

Low Density Lipoprotein

A total of 52 studies reported data on the effect of consumption of soy products on LDL levels. A wide range of effects were reported, ranging from –32 to +13 mg/dL (or –21% to +9%). While few studies found a statistically significant benefit of soy consumption, meta-analysis across the diverse studies yielded a statistically significant net change of –5 (95% CI –8 to –3) mg/dL (roughly –3%). Across studies, there is possible evidence that the beneficial effect of soy products increases with increasing baseline LDL, particularly among studies where mean baseline LDL was greater than 130 mg/dL; although these associations were not statistically significant. Similarly, there is possible evidence of an association between higher soy protein dose and greater net reduction in LDL; however, only in the sub-analysis of studies with elevated baseline LDL was this association statistically significant. When studies with minimal doses of soy protein (<10 g/day) were omitted, the association was non-significant. No association was found between soy isoflavone dose and net effect. Qualitative analysis across all studies revealed no other associations between net change and other variables, including differences among soy products, , soy incorporated into diet or as supplement, or population (post-menopausal women, pre-menopausal women, men). The 3 studies that compared effect to baseline LDL level came to conflicting conclusions. Most studies that directly compared different doses of soy protein or soy isoflavones found no significant difference in effect, although results were mixed. Most studies that also directly compared effect in men and women found no difference.

High Density Lipoprotein

A total of 56 studies reported data on the effect of consumption of soy products on HDL levels. The median net change compared to control found was +1 mg/dL. This estimate was in agreement with the meta-analysis estimate of +0.6 (95% CI –0.5, +1.8) mg/dL, which was not statistically significant. With only 2 exceptions, all studies reported a net effect on HDL of less than 10 percent, with an even distribution between net increases and net decreases or zero effect. Across studies, there were no consistent differences in effect based on baseline HDL, soy protein consumption, soy isoflavone consumption, soy incorporated into diet or as supplement, or population (post-menopausal women, pre-menopausal women, men). A possible associaton between baseline HDL and net change was found; although this association disappeared with the exclusion of 2 outlier studies. Studies that directly compared different baseline degree of abnormal lipids, doses of soy protein or soy isoflavones, or populations found no significant difference in effect.

Triglycerides

A total of 54 studies reported data on the effect of consumption of soy products on triglyceride levels. The median net change compared to control found was approximately –3 mg/dL (or –2%), although a wide range of effects were reported, ranging from –49 to +66 mg/dL (–49% to +31%). Meta-analysis estimated a significant net effect of –8 (95% CI –11, –5) mg/dL. Meta-regression revealed a possible association between increased mean baseline triglyceride level and greater net reduction in triglycerides. Neither isoflavone or soy protein dose was associated with net effect on triglycerides. Within specific studies that investigated these possible associations, though, most studies found no associations. There was no evident association with whether soy was incorporated into diet or as supplement, or based on population (post-menopausal women, pre-menopausal women, men).

Overall

There is a great deal of heterogeneity of effects found on lipoprotein and triglyceride levels. None of the factors we evaluated, including population, quality, applicability, soy isoflavone dose, soy protein dose, or baseline lipidemia level satisfactorily explained the heterogeneity. Overall, the majority of studies reported small to moderate effects on the lipids, despite a wide range of net effects for total cholesterol, LDL, and triglycerides. With few exceptions, studies consistently reported a small benefit on HDL. While we cannot exclude the possibility of publication bias (negative studies being less likely to be published) as an explanation for the effect of soy on LDL, there was no clear evidence that negative trials were "missing." However, the clinical heterogeneity of the trials makes this analysis difficult. Since most studies reported multiple outcomes, including lipids, it is possible that publication bias is less likely among these studies. It is also probably less likely that negative trials for HDL and triglycerides have not been published, unless the effect on LDL (and other outcomes) was also negative.

In order to guide future research, we have identified those studies that had a large effect on lipids. We arbitrarily defined "large" as an increase or decrease of at least 10 percent for total cholesterol, LDL, or HDL, and of at least 20 percent for triglycerides. We excluded studies with unequal baseline lipid levels between soy and control, studies with net improvements in subjects with normal baseline values, and studies with net worsening that resulted in still-normal lipid levels. These studies might provide insight into which formulations of soy product or which

populations may benefit or worsen lipid levels most. If such factors are discernible, it may be most worthwhile to focus future research on these factors.

Among randomized trials that compared soy products to non-soy controls, we identified 7 studies that reported large effects on lipids in 8 treatment arms. Three (4 arms) had net reductions of LDL ranging from 10 to 14 percent,[50,84,91] and 1 had a net reduction of total cholesterol of 12 percent.[61] We also identified 2 studies with large increases in triglycerides of 27 and 31 percent.[59,92] However, overall, there were no characteristics of these studies that distinguished them from studies with smaller or no effects on lipids.

Table 25. Number of studies included with different study designs (and total)

Randomized Design	Total Cholesterol	LDL	HDL	Triglycerides
Parallel	29	21	27	25
Cross-over	32	31	29	29
Total	**61**	**52**	**56**	**54**

HDL = high density lipoprotein; LDL = low density lipoprotein

Table 26. Number of studies included within each population and quality category, and within each baseline lipid and quality category

	Total Cholesterol				LDL				HDL				Triglycerides			
Quality / Population Category	Total	A 5	B 32	C 24	Total	A 4	B 28	C 20	Total	A 5	B 31	C 20	Total	A 5	B 27	C 22
Women & Men	**13**	0	7	6	**13**	0	7	6	**11**	0	6	5	**11**	0	6	5
Post-Menop Women & Men	**8**	0	6	2	**8**	0	6	2	**8**	0	6	2	**8**	0	6	2
Post-Menop Women	**24**	4	11	9	**20**	4	7	9	**23**	4	11	8	**22**	4	8	10
Peri-Menop Women	**3**	0	3	0	**3**	0	3	0	**3**	0	3	0	**3**	0	3	0
Pre-Menop Women	**3**	0	1	2	**2**	0	1	1	**2**	0	1	1	**2**	0	1	1
Men	**10**	1	4	5	**6**	0	4	2	**9**	1	4	4	**8**	1	3	4
Baseline Lipid Category																
Normal	**11**	0	4	7	**10**	0	4	6	**45**	3	27	17	**37**	3	18	16
Abnormal	**50**	5	28	17	**42**	4	24	14	**9**	2	4	3	**17**	2	9	6

HDL = high density lipoprotein; LDL = low density lipoprotein; Post-Menop = post-menopausal; Peri-Menop = peri-menopausal; Pre-Menop = pre-menopausal

Table 27. Number of studies (or study arms) included that used different types of soy products, controls, or soy consumption types (diet versus supplement)

	Total Cholesterol	LDL	HDL	Triglycerides
Soy Product (Study Arms)				
Protein with Isoflavones	67	57	63	60
Protein without Isoflavones	11	10	11	11
Isoflavones	11	9	10	10
Control Types (Study Arms)				
Dairy	32	30	30	28
Animal/Usual Diet	10	8	8	8
Placebo	10	8	9	9
Miscellaneous	8	6	8	7
No Non-Soy Control	5	5	5	5
Diet or Supplement (Studies) [a]				
Diet	24	17	22	20
Supplement	38	35	35	35

HDL = high density lipoprotein; LDL = low density lipoprotein

[a] One study is double counted because it compares diet to supplement.

Table 28. Number of studies that directly compared the effects of different soy product characteristics or study subject characteristics

Comparison Characteristics	Total Cholesterol	LDL	HDL	Triglycerides
Protein with *v* without Isoflavones [a]	11	10	11	11
Different Soy Protein Dosages	4	3	4	4
Different Soy Isoflavone Dosages	14	12	14	14
Different Baseline LDL or TC Levels	3	4	2	3
Different Population Categories	4	4	4	4

HDL = high density lipoprotein; LDL = low density lipoprotein; TC = total cholesterol

[a] One study also included an isoflavone only treatment arm (for all lipids).

3.2.7. Lipoprotein(a)

(Tables 29-31)

Lipoprotein(a) [Lp(a)] is a low density lipoprotein (LDL)-like particle in which an apolipoprotein(a) [apo(a)] moiety is linked to apolipoprotein B-100. Lp(a) is an acute-phase reactant and has been postulated to be a highly atherothrombotic protein. The concentration of Lp(a) is under genetic control and varies among individuals depending on the apo(a) isoform. Diet and exercise have little influence on Lp(a) concentration. The only treatment to lower Lp(a) levels that has been shown to be effective is hormone replacement therapy in post-menopausal women.

Study Descriptions

We found 20 eligible studies, of which 18 reported numerical data on Lp(a) and are summarized here;[49,52,55,57,64,71,74,77,78,80,82,83,86,89,90,106,109,110] the remaining 2 did not report data.[51,98] Among these, 17 studies were RCTs – including 10 cross-over trials – and 1 was a non-randomized trial. Studies evaluated concentrations of Lp(a) after soy product consumption for 4 weeks to 1 year. Seven studies were conducted among post-menopausal women only, 4 studies included men only, and 7 studies included both men and women. One of these evaluated women with treated breast cancer, and one evaluated men and women with diabetes mellitus. Seven studies evaluated soy diets (Table 29); 9 evaluated soy protein supplements (Table 30); and 2 evaluated soy isoflavone supplements (Table 31).

Studies reported Lp(a) using different metrics, and we found several inconsistencies in reporting. The majority of the studies were assessed to a quality score of C (3 A, 3 B, 12 C) and were applicable to healthy, and/or breast cancer treated post-menopausal women and middle-aged hypercholesterolemic men. All studies had generally limited applicability even within categories.

Overall Effect

The large majority of studies reported non significant changes in Lp(a) from baseline after soy intervention. Among 18 studies, 2 found a net decrease of at least 4 mg/dL (or a statistically significant decrease) in Lp(a) concentration, 4 found a net increase of at least 4 mg/dL (or a statistically significant increase), and 12 found no effect. Only 3 studies reported significant or near significant net changes in Lp(a) after soy protein consumption compared to controls. Nilausen 1999[109] (Table 29) reported a non-significant change in Lp(a) among men consuming soy, but a significant decrease in Lp(a) among controls consuming caseinate; this resulted in a statistically significant net increase in Lp(a). Teede 2001[77] (Table 30) found a substantially greater, statistically significant, increase in Lp(a) among men and post-menopausal women supplemented with soy product compared to casein. Dent 2001[82] (Table 30), reported a marginally significant net decrease in median Lp(a) among hypercholesterolemic peri-menopausal women supplemented with soy product with and without isoflavone compared to whey protein.

Soy Product, Dose, Other Variables

No study directly compared different soy products. The studies evaluated dietary tofu, soy protein isolate diet, soybean, bean sprout and soy flour diet, and isoflavone supplements with

and without soy protein. Across the studies, there is no discernable difference in effect based on the type of soy product.

Likewise, there was no consistent difference across studies in effect based on either quantity of soy protein or quantity of isoflavones. Six studies[49,52,80,82,86,106] directly compared soy products with different levels of isoflavones ranging from 1 mg/day to 185 mg/day. All studies found no significant effect (within-cohort or net effect) regardless of isoflavone dose.

Two studies directly compared soy products with different amounts of soy protein.[52,80] Both Teixera 2000[52] (Table 29) who compared 4 doses between 20 and 50 mg/day in men, and Tonstad 2002[80] (Table 30)who compared 30 and 50 mg/day in men and post-menopausal women found no significant relationship between soy protein dose and effect on Lp(a).

Jenkins 2002[49] (Table 29) also analyzed the effect of soy products in men and women separately (data not displayed in summary table) and reported no significant effect between sexes. Meyer 2004[71] performed sub analysis based on the production of equol, and reported significantly lower Lp(a) concentration among equol-positive subjects after the consumption of soy diet (data not displayed in summary table), which according to the authors suggested that changes in Lp(a) might have been linked to equol.

Summary

A total of 18 studies reported data on the effect of consumption of soy products on Lp(a) concentration. Overall, across studies, there were no discernable differences in effect based on soy protein consumption, soy isoflavone consumption, soy incorporated into diet or as supplement, or population (post-menopausal women, pre-menopausal women, men). However, 2 studies reported significant increase in net effect of soy consumption on Lp(a) concentration. Based on the limited evidence, no definite conclusions can be made on the Lp(a)-raising effect of soy protein consumption.

Table 29. Effect of soy product diets on lipoprotein (a) (mg/dL)

Diet/Supplement	Design	Control	Dose							Change			Net Change [a]				
			mg/day				g/day										
Author Year	Duration	Intervention	Genistein	Daidzein	Glycitein	T Isoflav	Soy Protein	N	Base value	Value	P within	P btw Soy	Value	P vs Control	Population	Applicability	Quality
Diet	Xover	Dairy															
Jenkins 2002 12145008	4 wk	ISP w/Isoflavones				73	50	41	19.2	*+0.9*		NS	*-1.1*	NS	post♀ ♂		C
		ISP w/Isoflavones				10	52		20.2	*+1.5*			*-0.5*	NS			
		Low fat dairy+egg protein							19.6	*+2.0*							
Nilausen 1999	4.5 wk	ISP w/Isoflavones, liquid					154	9	12.7 [b]	*-2.7*	NS		*+4.5*	<0.002 [c]	♂		C
		Calcium caseinate							12.0 [b]	*-7.2*	<0.0002						
Diet	RCT	Dairy															
Teixeira 2000	6 wk	ISP w/Isoflavones				95	50	15	30.9 [d]	-7.0 [e]	NS	nd	*-4.6*	NS	♂		A
		ISP w/Isoflavones				76	40	17	25.5 [d]	-4.8 [e]	NS		*-1.2*	NS			
		ISP w/Isoflavones				57	30	18	26.8 [d]	-16.8 [e]	NS		*-13.2*	NS			
		ISP w/Isoflavones				38	20	15	23.0 [d]	-11.3 [e]	NS		*-7.7*	NS			
		Calcium caseinate						16	17.8 [d]	-3.6 [e]	NS						
Vigna 2000	12 wk	ISP w/Isoflavones				76	40	40	16 [f]	+1 [g]	NS		*-2* [g]		post♀		C
		Caseinate						37	17 [f]	+3 [g]	NS						
Diet	Xover	Animal/Usual															
Ashton 2000 11194529	4 wk	ISP diet	84	35		120	36	42	nd	24.5 [h]			-0.8	NS [c]	♂		C
		Lean meat diet								25.3 [h]							
Diet	Xover	Miscellaneous															
Jenkins 1999	4 wk	ISP diet					33	30	31.8 [j]	*-0.7*			*-1.5*	NS	post♀ ♂		C [k]
		Vegetarian diet							28.8 [j]	*+0.8*							
Diet	NRCT	No Control															
Yildirir 2001	6 wk	ISP diet					20	20	23.4	*-1.2*	NS		--		♂		C
		No control group						--									

Apparent discrepancies between Within-Cohort changes and Between-Cohort changes are due to rounding errors in estimated Within-Cohort changes compared to reported Between-Cohort changes.

[a] Or difference between final values, as noted.
[b] Graph.
[c] Difference of final values (cross-over study)
[d] Median. Reported in nmol/L; values divided by 2.4 (nmol/L per mg/dL).
[e] Mean change, adjusted for baseline value.
[f] Median.
[g] Difference or net difference of median values.
[h] Final values (baseline values not reported).
[j] Units reported to be mgl/L; however values most consistent with mg/dL.
[k] In contrast to other outcomes in this article, units for Lp(a) unclear.

Table 30. Effect of soy protein supplements on lipoprotein (a) (mg/dL)

Diet/Supplement	Design	Control	Dose (mg/day)				Dose (g/day)			Change			Net Change [a]				
Author Year	Duration	Intervention	Genistein	Daidzein	Glycitein	T Isoflav	Soy Protein	N	Base value	Value	P within	P btw Soy	Value	P vs Control	Population	Applicability	Quality
Supplement	Xover	Dairy															
Meyer 2004	5 wk	Soy milk/yogurt				80	30	23	26.0	*+1.2*			-0.9	NS [b]	post♀♂		B
		Low fat milk/yogurt								*+0.8*							
Hermansen 2001	6 wk	ISP w/Isoflavones				>165	50	20	29.5 U/L	*+4.4*			*+4.3*	NS	♀♂ DM		C
		Casein							32.3 U/L	*+0.1*							
Supplement	RCT	Dairy															
Teede 2001	13 wk	ISP w/Isoflavones	77	38	5	118	40	86	28.6 [c]	+42			*+38*	<0.05	post♀♂		B
		Casein						93	34.1 [c]	+4							
Kreijkamp-Kaspers 2004	52 wk	ISP w/Isoflavones	52	41	6		26	88[d]	27	*+4*			+3	NS	post♀		A
		Total milk protein						87[d]	24	*0*							
Tonstad 2002	16 wk	ISP w/Isoflavones				185	50	31	41.7	*+8.1*		nd	+2.5	NS	post♀♂		B
		ISP w/Isoflavones				111	30	34	43.7	*+4.5*							
		Casein, 50 g						29	36.7	*+12.2*							
		Casein 30 g						36	40.5	*+3.8*							
Dent 2001	24 wk	ISP w/Isoflavones				80	40	24	8 [e]	*0* [f]	NS	NS	*-10* [f]	0.052	peri♀		B
		ISP w/o Isoflavones				4	40	24	8 [e]	*0* [f]	NS		*-10* [f]				
		Whey protein						21	11 [e]	*+10* [f]							
Puska 2002	6 wk	ISP w/Isoflavones				96	52	24	27.2 [g]	+5.7			+4.4	NS	post♀♂		C
		Calcium caseinate						24	34.1 [g]	+1.4							
Supplement	Xover	No Control															
Merz-Demlow 2000	13 wk	ISP w/Isoflavones	70	47	10	128	53	13	nd	+14.6 [h]		NS	--		pre♀		C
		ISP w/Isoflavones	35	24	5	64	53			+15.2 [h]			--				
		ISP w/o Isoflavones	5	4	1	10	53			+14.6 [h]			--				
		No control group						--									
Wangen 2001	13 wk	ISP w/Isoflavones	70	47	10	128	53	18	nd	*27.4* [j]		NS [b]	--		post♀		C
		ISP w/Isoflavones	35	24	5	64	53	17		*27.2* [j]			--				
		ISP w/o Isoflavones	5	4	1	10	53	18		*26.8* [j]			--				
		No control group						--									

Apparent discrepancies between Within-Cohort changes and Between-Cohort changes are due to rounding errors in estimated Within-Cohort changes compared to reported Between-Cohort changes.

[a] Or difference between final values, as noted.
[b] Difference of final values (cross-over study)
[c] Mean of log transformed values.
[d] Intention-to-treat analysis (75 completed soy protocol, 78 completed control protocol)
[e] Median. Graph. Reported in nmol/L; values divided by 2.4 (nmol/L per mg/dL).
[f] Difference or net difference of median values.
[g] Units reported to be g/L; however values most consistent with mg/L.
[h] Reported as "Effect" and least-squared mean. Vague if these values truly represent within-cohort changes.
[j] Final values (baseline values not reported).

Table 31. Effect of soy isoflavones (without soy protein) on lipoprotein (a) (mg/dL)

Diet/Supplement	Design	Control	Dose														
			mg/day				g/day				Change		Net Change [a]				
Author Year	Duration	Intervention	Genistein	Daidizein	Glycitein	T Isoflav	Soy Protein	N	Base value	Value	P within	P btw Soy	Value	P vs Control	Population	Applicability	Quality
Supplement	Xover	Placebo															
Nikander 2004 15240647	13 wk	Isoflavones	6	42	66		0	56	17.1	+0.9	NS		*+1.8*	NS	post♀ Breast CA	🧍	A
		Placebo							17.6	-0.9	NS						
Simons 2000	8 wk	Isoflavones				80	0	20	nd	16.6 [b]			*-1.3*	NS [c]	post♀	🧍	C [d]
		Placebo								17.9 [b]							

Apparent discrepancies between Within-Cohort changes and Between-Cohort changes are due to rounding errors in estimated Within-Cohort changes compared to reported Between-Cohort changes.

[a] Or difference between final values, as noted.
[b] Final values (baseline values not reported).
[c] Difference of final values (cross-over study)
[d] In contrast with other outcomes in this article, no baseline Lp(a) value was reported.

3.2.8. Blood Pressure

(Tables 32-35, Figure 10)

Blood pressure (BP) reduction is associated with decreased CVD, kidney disease, and mortality. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High blood pressure (JNC 7) recognizes the relationship of increased risk for CVD for each increment of 20 mm Hg of systolic BP or 10 mm Hg of diastolic BP across the range of 115-185/75-115 mm Hg.[111] This has led to the new classification of pre-hypertension as well as recommendation of health promoting lifestyle modifications for systolic BP >120 mm Hg or diastolic BP >80 mm Hg. Population studies have demonstrated an inverse relationship between dietary protein intake and blood pressure.[112,113]

Study Descriptions

Among 25 eligible studies, we found 22 studies that reported numerical data on BP, which are summarized here;[23,24,49,55,62,64,65,69,71,74,76,77,79,84,90-92,114-118] the remaining 3 reported only no significant effect.[48,73,89] Only one study included subjects with a mean baseline systolic BP less than 120 mm Hg. Therefore, we have categorized those studies with mean baseline systolic BP under 140 mm Hg as "pre-hypertension." We have categorized them into separate tables as follows: 4 studies included subjects whose mean baseline blood pressure was greater than 140/90 mm Hg (hypertension) (Table 32); and 18 studies of subjects with mean blood pressure less than 140/90 mm Hg (pre-hypertension), of which 6 evaluated soy product diets (Table 33); 8 evaluated soy product supplements (Table 34); and 4 evaluated soy isoflavones (Table 35).

All 18 studies that included subjects with pre-hypertension were RCTs including 9 cross-over trials. Studies evaluated BP changes after soy product consumption for 4 weeks to 6 months. The majority of studies included post-menopausal women. Notably, Burke 2001[117] (Table 33) evaluated men and women diagnosed with hypertension and were receiving anti-hypertensive medication that was successfully controlling their BP.

The studies of hypertensive subjects included 2 RCTs, 1 trial with no control for soy, and 1 prospective cohort study. Two studies evaluated BP changes after soy product consumption for 8 weeks and two after 12 weeks. The study populations included men and women with chronic kidney disease, men with moderate hypertension, and post-menopausal women with diabetes mellitus.

The range of daily soy isoflavone intake among studies of soy products with isoflavones was approximately 10 to 165 mg, with a median of 80 mg per day. The range of daily soy protein intake among relevant studies was approximately 14 to 66 g, with a median of 33 g per day. The majority of studies were assessed to a quality score of B (3 A, 12 B, 6 C). Most studies included post-menopausal women; few included men and women. Ten studies have narrow applicability, 6 moderate applicability, and 6 broad applicability.

Overall Effect

Across the 22 studies, all but one (Rivas 2002,[116] Table 32) reported similar effects of soy products on systolic or diastolic BP, within the range of –7 to +5 mm Hg systolic BP and –5 to +4 mm Hg diastolic BP.

The summary estimates from random-effects model meta-analyses of all soy cohorts with a non-soy control for systolic and diastolic BP were not statistically significant (Figure 10). The net change in systolic BP was –1 (95% CI –3 to +1) mm Hg, where the summary mean baseline systolic BP was approximately 132 mm Hg. The net change in diastolic BP was –1 (95% CI –2 to +0) mm Hg, where the summary mean baseline DBP was approximately 80 mm Hg.

As noted, however, the study by Rivas 2002[116] was clearly an outlier with a substantially greater (and statistically significant) net reduction in both systolic and diastolic BP. Exclusion of this study resulted in a meta-analysis of now statistically homogeneous studies. As shown in Figure 10, though, exclusion of this outlier study did not greatly affect the summary estimate of net effect.

Rivas 2002[116] (Table 32) included both men and women with moderate essential hypertension, half of whom were untreated hypertensives; the remainder had a 4 week washout period without anti hypertensive medications. The authors attributed the beneficial effect of the intervention on BP level to the twice daily consumption of natural soy milk high in soy protein and isoflavones. However, the other study with twice-daily dosing (Washburn 1999,[23] Table 34) did not find a similarly large effect. While there was a statistically significant reduction in diastolic blood pressure with twice daily soy, the magnitude of the effect was similar to that for once daily soy. In addition, the Rivas 2002[116] study did have potential flaws because of substantial differences in fat and carbohydrate composition between the soy and control arm; although this was a common flaw among studies.

Soy Product, Dose, Other Variables

The studies evaluated a wide range of soy products including soybean diet, soymilk, and isoflavone supplements with and without soy protein. Only 2 studies directly compared different soy products or regimens. Jenkins 2002[49] (Table 33) compared the effect of soy products with different levels of isoflavones (73 mg vs 10 mg) and found no apparent difference in effect. Washburn 1999[23] (Table 34) compared the same dose of isoflavone supplements as single and split doses and reported a significant decrease in diastolic BP after split dose consumption of isoflavone supplement, although there was no statistical difference between the 2 regimens.

Only Jenkins 2002[49] (Table 33) compared BP effect in men and women. In response to soy consumption, there was a significant difference between men and women only for systolic BP. Analysis of the sexes separately indicated a tendency to lower systolic BP for men during the high-isoflavone soy phase, but a significant decrease during the low-isoflavone soy phase compared to the control phase.

As expected due to the statistical homogeneity among studies (bar Rivas 2002[116]), meta-regression and sub-analyses failed to find associations between effect and baseline BP or soy dose. Among the 18 studies of subjects with pre-hypertension, 5 found a net decrease of at least 3 mm Hg (or a statistically significant decrease) of either systolic or diastolic BP, 3 found a net increase of at least 3 mm Hg of either systolic or diastolic BP, and 10 found no effect. Only 4 studies found significant or near significant reductions of systolic and/or diastolic BP after soy protein consumption compared to controls. Burke 2001[117] (Table 33), and Teede 2001[77] (Table 34) reported significant reductions in BP with soy protein consumption compared to controls. Washburn 1999[23] (Table 34) reported a significant decrease in diastolic BP from baseline in healthy peri-menopausal women during one phase of soy protein consumption compared to controls, but no significant effect on systolic BP. Sagara 2004[65] (Table 33) reported a significant

decrease in BP compared to baseline and a near significant decrease in systolic BP compared to controls.

One recent study[118] by Kreijkamp-Kaspers 2005 (Table 34), reported a trend towards increase in BP from baseline during soy protein consumption in post-menopausal women. The study also reported a statistically significant net increase in systolic BP compared to controls, but no significant effect on diastolic BP. Women consuming soy protein had a net increase, but a non-significant increase in systolic BP, when those taking anti-hypertensive medications were excluded from the analyses.

Summary

A total of 22 studies with mostly moderate quality reported data on the effect of consumption of soy products on systolic and diastolic BP. Overall, soy consumption does not appear to affect BP level. Across studies there were no discernable differences in effect based on baseline BP, soy protein consumption, soy isoflavone consumption, soy incorporated into diet or as supplement, or population (post-menopausal women, pre-menopausal women, men). The one outlier study attributed its large beneficial effect to twice daily consumption of soy protein. However, a separate study comparing once to twice daily soy found similar effects.

Table 32. Effect of soy products on blood pressure (mm Hg) in subjects with hypertension (Baseline SBP>140 or DBP>90)

Diet/Supplement	Design	Control	Dose								Change			Net Changee				
			mg/day				g/day											
Author Year	Duration	Intervention	Genistein	Daidizein	Glycitein	T Isoflav	Soy Protein	N	Base value SBP DBP		Value	P within	P btw Soy	Value	P vs Control	Population	Applicability	Quality
Diet	NRCT	No Control																
Gentile [a b] 1993	8 wk	ISP diet					0.7-0.8 g/kg bw [c]	20	141 89		*+1* *-2*	NS NS		-- --		♀♂ CKD		C
		No control group						--										
D'Amico [a b] 1992	8 wk	ISP diet					0.7-0.8 g/kg bw [c]	20	143		*-2*	NS		--		♀♂ CKD		C
		No control group						--										
Supplement	RCT	Dairy																
Rivas[d] 2002	12 wk	Soy milk	80	63		140	18	20	155 100		-18.4 -15.9	<0.0001 <0.0001		*-17.0* *-12.2*		♀♂ HTN[d]		B
		Milk							152 99		-1.4 -3.7	NS NS						
Supplement	Xover	Miscellaneous																
Jayagopal 2002	12 wk	ISP w/Isoflavones	70	49	13	132	30	29	147 82		-1.1 -0.3			-3.5 *+0.1*	NS [d] NS [d]	post ♀ DM		B
		Cellulose							147 83		+2.4 -0.2							

Apparent discrepancies between Within-Cohort changes and Between-Cohort changes are due to rounding errors in estimated Within-Cohort changes compared to reported Between-Cohort changes.

[a] Randomized cross-over trial, but not relevant control group (soy + fish oil)
[b] Same cohort, different study periods with different types of intervention
[c] bw: ideal body weight
[d] Subjects with hypertension: 50% treated and 50% untreated
[e] Or difference between final values, as noted.

Table 33. Effect of soy product diets on blood pressure (mm Hg) in subjects with pre-hypertension (Baseline SBP<140 or DBP<90)

Diet/Supplement	Design	Control	Dose								Change			Net Changef				
			mg/day				g/day											
Author Year	Duration	Intervention	Genistein	Daidzein	Glycitein	T Isoflav	Soy Protein	N	Base value SBP DBP	Value	P within	P btw Sex	Value	P vs Control	Population	Applicability	Quality
Diet	Xover	Dairy															
Jenkins 2002 12145008	4 wk	ISP w/Isoflavones				73	50	41	123 78	*-1.0* *-1.0*		NS[a]	*+1.0* *-1.0*		post♀ ♂	↑	C
		ISP w/Isoflavones				10	52		124 78	*-4.0* *-2.0*			*-2.0* *-2.0*				
		Low fat dairy + egg protein							125 78	*-2.0* *0*							
Diet	RCT	Dairy															
Vigna 2000	12 wk	ISP w/Isoflavones				76	40	51/40[d]	127 82	-3.2 -0.1	NS NS		*+5.4* *+3.0*		post♀	↑	C
		Caseinate						53/37[d]	130 83	-8.6 -3.1	NS NS						
Diet	RCT	Animal/Usual															
Chiechi 2002 11836040	26 wk	ISP diet				47		58/24[d]	132 81	-3.4 +0.2	NS NS		*-0.3* *-2.6*		post♀	↑	C
		Usual diet						55/43[d]	130 81	-3.1 +2.8	NS NS						
Diet	Xover	Miscellaneous															
Jenkins 1999	4 wk	ISP diet					33	30	120 79	*+1.0* *-2.0*			*+1.6* *+1.7*	NS[b] NS[b]	post♀ ♂	↑	B
		Vegetarian diet							120 80	*-1.0* *-4.0*							
Diet	RCT	Miscellaneous															
Sagara 2004	5 wk	Soy powder baked goods				80	20	25	142 87	*-11* *-5*	<0.01 <0.01		-7 *-3*	0.05[c] NS	♂	↑	B
		Usual baked goods						25	134 81	*-4* *-2*	NS NS						
Burke[e] 2001	8 wk	ISP w/psyllium					66	9	135 74	*-8.4* *-2.3*		nd	-5.9 -2.6	0.001 0.006	♀♂ HTN[e]	↑	B
		ISP					66	9	134 77	*-0.1* *-1.0*							
		Psyllium w/maltodextrin						9	132 78	*-0.5* *+0.6*							
		Maltodextrin						9	132 75	*+2.3* *+1.4*							

Apparent discrepancies between Within-Cohort changes and Between-Cohort changes are due to rounding errors in estimated Within-Cohort changes compared to reported Between-Cohort changes.

[a] Significant differences between the sexes (Women/Men)
[b] Difference of final values (cross-over study)
[c] Net change reported non-significant in the text
[d] N: baseline/final
[e] All patients had hypertension and were on antihypertensive medications and successfully controlled baseline BP
[f] Or difference between final values, as noted.

Table 34. Effect of soy product supplements on blood pressure (mm Hg) in subjects with pre-hypertension (Baseline SBP<140 or DBP<90)

Author Year	Duration	Intervention	Dose mg/day Genistein	Daidzein	Glycitein	T Isoflav	g/day Soy Protein	N	Base value SBP DBP	Change Value	Change P within	Change P btw Soy	Net Change!!! Value	Net Change!!! P vs Control	Population	Applicability	Quality
Diet/Supplement	**Design**	**Control**															
Kurowska 1997	4 wk	Soy milk					31	34	131 77	*-3.0* *0* *-8.0* *-4.0*	0.04 0.02 0.04 0.02		*+5.0* *+4.0*		♀♂	↑	B
		Milk, 2% fat															
Meyer 2004	5 wk	Soy milk/yogurt				80	30	23	132 77	*0* *0* *+1.0* *+2.0*			-0.6 -2.0	NS [a] NS [a]	post♀♂	↑	B
		Low fat milk/yogurt															
Hermansen 2001	6 wk	ISP w/Isoflavones				>165	50	20	130 78	*0* *0* *-1.0* *0*	NS NS NS NS		*+1.0* *0*	NS [a] NS [a]	♀♂ DM	↑	C
		Casein															
Cuevas 2003	8 wk	ISP w/Isoflavones	48	24	8	80	<40	18	132 73	*-5.0* *-3.0* *-5.0* *-4.0*	NS NS NS NS		*0* *+1.0*		post♀	↑	B
		Caseinate															
Supplement	**RCT**	**Dairy**															
Kreijkamp-Kaspers 2005	52 wk	ISP w/Isoflavones	52	41	6		26	88 [b]	138 74	*+0.8* *+0.3*			*+4.3* *+2.0*	0.04 NS	post♀	↑	A
		Total milk protein						87 [b]	143 76	*-3.5* *-1.7*							
		ISP w/Isoflavones	52	41	6		26	75	137 73	*-0.1* *-0.7*			*+3.8* *+1.1*	NS NS	post♀ No Rx [c]		
		Total milk protein						63	140 74	*-3.9* *-1.9*							
Teede 2001	13 wk	ISP w/Isoflavones	77	38	5	118	40	86	130 76	-7.5 -4.3			*-3.9* *-2.4*	<0.05 [a] <0.05 [a]	post♀♂	↑	B
		Casein						93	128 76	-3.6 -1.9							
Puska 2004	8 wk	ISP				153	41	69	130 81	*0* *0*			*+1.0* *0*		post♀♂	↑	B
		Yogurt						74	132 81	*-1.0* *0*							
Supplement	**Xover**	**Miscellaneous**															
Washburn 1999	6 wk	ISP w/Isoflavones once daily				34	14	42	132 82	*-8.0* *-6.0*		NS	*-2.0* *-3.0*	NS [a] NS [a]	peri♀	↑	B
		ISP w/Isoflavones twice daily				34	14			*-7.0* *-8.0*			*-1.0* -4.9	NS [a] <0.01 [a]			
		Carbohydrates								*-6.0* *-3.0*							

Apparent discrepancies between Within-Cohort changes and Between-Cohort changes are due to rounding errors in estimated Within-Cohort changes compared to reported Between-Cohort changes.

[a] Difference of final values (cross-over study)
[b] Intention-to-treat analysis (75 completed soy protocol, 78 completed control protocol)
[c] Excluding women who were taking anti-hypertensives

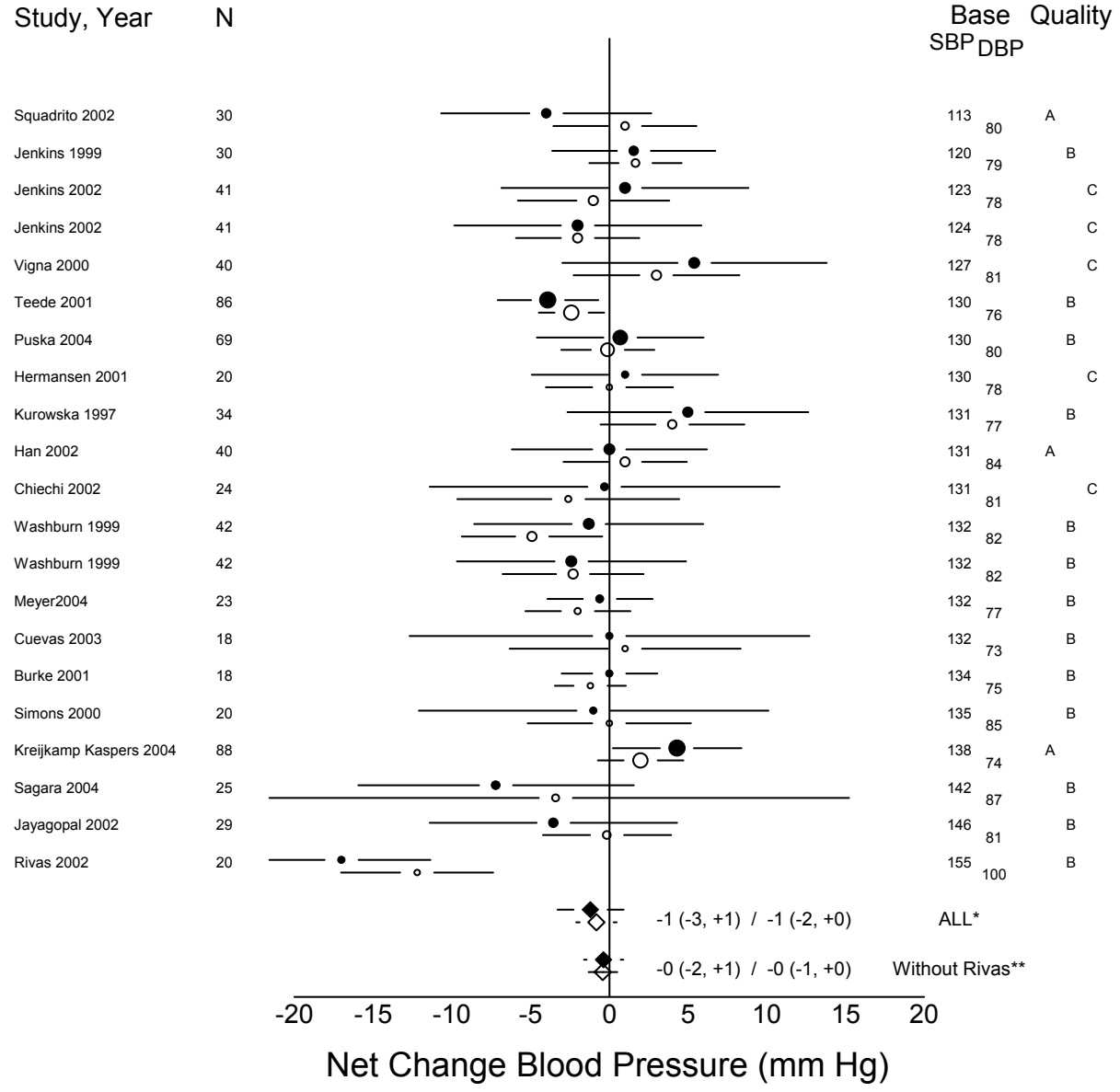
Table 35. Effect of soy isoflavones (without soy protein) on blood pressure (mm Hg) in subjects with pre-hypertension (Baseline SBP<140 or DBP<90)

Diet/Supplement	Design	Control	Dose						Base value	Change			Net Change!!!				
			mg/day				g/day										
Author Year	Duration	Intervention	Genistein	Daidizein	Glycitein	T Isoflav	Soy Protein	N	SBP DBP	Value	P within	P btw Soy	Value	P vs Control	Population	Applicability	Quality
Supplement	Xover	Placebo															
Nestel[b] 1997	5 wk	Isoflavones	45	35	3	80	0	21	MAP	*-6*	<0.05		*0*	NS [a]	post♀	🚹	C
		Placebo							86	*-6*	<0.05						
Simons 2000	8 wk	Isoflavones				80	0	20	135	*-10.0*			*-1.0*	NS [a]	post♀	🚹	B
									82	*-2.0*			*0*	NS [a]			
		Placebo								*-9.0*							
										-2.0							
Supplement	RCT	Placebo															
Han 2002	13 wk	Isoflavones	70	19	11	100	0	40	131	*0*	NS		*0*		post♀	🚹🚺	A
									84	*+1.0*	NS		*1.0*				
		Placebo						40	133	*0*	NS						
									84	*0*	NS						
Squadrito[b] 2002	26 wk	Genistein	54				0	30	113	*-3.0*	NS		*-4.0*	NS	post♀	🚹🚺	A
									80	*-1.0*	NS		*-2.0*	NS			
		Placebo						30	112	*+1.0*	NS						
									77	*+1.0*	NS						

Apparent discrepancies between Within-Cohort changes and Between-Cohort changes are due to rounding errors in estimated Within-Cohort changes compared to reported Between-Cohort changes.

[a] Difference of final values (cross-over study)
[b] Studies with normal baseline blood pressure

Figure 10. Meta-analysis of the effect of soy products on systolic (SBP) and diastolic blood pressure (DBP) in all randomized trials with non-soy controls. Circles represent net effect on BP of individual study cohorts vs. non-soy controls; their size is proportional to the square root of the sample size. Diamonds represent summary mean net changes using a random effects model meta-analysis (and sub-analysis). Bars (and values in parentheses) represent 95% confidence intervals. Black symbols represent SBP, open symbols represent DBP. Cohorts are ordered from lowest (top) to highest mean SBP. N indicates sample size of subjects consuming soy products. Blood pressure units are mm Hg.
*** Effect is heterogeneous across all studies.**
**** Effect is homogeneous across studies when Rivas 2002 excluded.**



3.2.9. C-Reactive protein

(Table 36)

C-reactive protein (CRP) is an acute phase reactant, and a protein synthesized by the liver. CRP in the upper range (>3.0 mg/L) assessed by the automated high sensitivity assays (hs-CRP) has been shown to be an independent and high risk factor for CVD.[119] CRP levels increase in acute and chronic inflammatory states. Conventional conjugated estrogen replacement therapy has shown to increase CRP levels.[120] Given the theory that soy phytoestrogens may have estrogenic activity, it is of interest whethersoy consumption may affect CRP levels.

Study Descriptions

We found 3 eligible studies that all reported data on hs-CRP.[121-123] All studies were RCTs including 2 cross-over trials. Two studies evaluated CRP levels after soy product consumption for 13 weeks, and one study after 4 weeks. All 3 studies were conducted among post-menopausal women. One of these evaluated women with treated breast cancer. One study also included hypercholesterolemic men.

All studies were assessed to a quality score of B/C. One study included both men and post-menopausal women (who were analyzed separately); one included only post-menopausal women; and the third study was restricted to post-menopausal women with a history of treated breast cancer.

Overall Effect

No study found a significant effect of soy protein consumption on CRP level. Two studies reported trends towards increases in CRP levels from baseline among women after soy intervention, but these effects were non-significant compared to controls. However, the rise in CRP levels was not seen in the sub-analysis of men.

Soy Product, Dose, Other Variables

No study directly compared different soy products. The 3 studies evaluated dietary tofu, soy protein isolate diet, and isoflavone supplements. Across the small number of studies, there is no discernable difference in effect based on the type of soy product.

Likewise, there was no consistent difference across studies in effect based on either quantity of soy protein or quantity of isoflavones. Jenkins 2002[121] compared soy products with differing amounts of isoflavones. Changes in CRP were similar in both soy arms in this study.

Only Jenkins 2002[121] analyzed the effect of soy products in both men and women. Although CRP levels rose in the soy arms in women (both within-cohort and compared to control) and decline in men, none of the changes was statistically significant.

Summary

Few studies have evaluated the effect of soy consumption on CRP level. The limited data available suggest that there is no effect on CRP level by the consumption of soy products.

Table 36. Effect of soy products on C-reactive protein (mg/L)

Diet/Supplement	Design	Control	Dose										Change		Net Change				
			mg/day				g/day												
Author Year	Duration	Intervention	Genistein	Daidzein	Glycitein	T. Isoflav	Soy Protein	N	Base value	Value	P within	P btw Soy	Value	P vs Control	Population	Applicability	Quality
Diet	Xover	Dairy															
Jenkins 2002 12077742 [a]	4 wk	ISP w/Isoflavones				73	50	23	2.5	-0.5		ND	*-0.9*	*NS* [b]	♂	👥	C
		ISP w/Isoflavones				10	52		3.5	-1.0			*-1.4*	*NS* [b]			
		Low fat dairy + egg protein							1.6	+0.4							
		ISP w/Isoflavones				73	50	18	2.8	+1.7		ND	*+2.4*	*NS* [b]	post♀		
		ISP w/Isoflavones				10	52		2.4	+0.7			*+1.4*	*NS* [b]			
		Low fat dairy + egg protein							3.4	-0.7							
Supplement	RCT	Dairy															
Teede 2004	13 wk	ISP w/Isoflavones	77	38	5	118	52	30	1.91	+0.42	<0.05		*-0.06*	NS	post♀	👥	B
		Casein						20	1.39	+0.48	<0.05						
Supplement	Xover	Placebo															
Nikander 2003 14602747	13 wk	Isoflavones	6	42	66	114	0	56	1.16	-0.06	NS		*-0.06*	NS [b]	post♀ Breast CA	🧍	A
		Placebo							1.10	0	NS						

Apparent discrepancies between Within-Cohort changes and Between-Cohort changes are due to rounding errors in estimated Within-Cohort changes compared to reported Between-Cohort changes.

[a] Data available only for women and men separately
[b] Difference of final values (cross-over study)

3.2.10. Homocysteine

(Table 37)

Increased homocysteine levels are associated with atherosclerotic disease and may induce vascular injury by primary atherogenic and prothrombotic effects. High homocysteine levels are an independent emerging risk factor for atherosclerotic vascular disease,[124] but its optimal use in screening and risk stratification has yet to be determined. To date, no treatment has been shown to lower homocysteine levels. Therefore, it is of interest whether consumption of soy products may effect homocysteine levels.

Study Descriptions

We found 5 eligible studies that reported data on homocysteine;[49,74,79,80,83] all randomized controlled trials, including 2 cross-over trials. Four studies had soy supplements and 1 had diet for the soy intervention; all studies compared to dairy for the control arm. The duration of intervention ranged from 4 to 16 weeks, with a range of 20 to 69 subjects in the soy intervention arm. All studies were assessed to a quality score of B/C. All studies included both men and (generally post-menopausal) women, one of which restricted inclusion to people with diabetes mellitus. The studies were assessed to have an applicability of 1 to 3.

Overall Effect

All but 2 studies[74,79] reported a decrease in homocysteine levels from baseline after soy consumption. All studies except Puska 2004[79] reported a significant decrease in homocysteine levels after the soy consumption when compared to control arm.

Soy Product, Dose, Other Variables

The studies evaluated tofu diet, isolated soy protein diet, and isoflavone supplements with soy protein. Only 2 studies[49,80] compared different soy products. Jenkins 2002[49] compared the effect of soy products with differing amounts of isoflavones (73 mg vs. 10 mg) and found no apparent difference in effect. The same study also compared effect of soy products in men and women and found no apparent difference in effect between genders.

Tonstad 2002[80] combined the effect of 2 isolated soy proteins with different levels of isoflavones (185 mg vs. 111 mg) and compared to the 2 dairy groups to assess the net treatment effect.

Three studies[79,80,83] used the same type of isoflavone, and only 2 studies[80,83] found a significant decrease in homocysteine levels after the soy consumption; Puska 2004[79] reported a non-significant effect.

Summary

Only 5 studies of moderate to poor quality reported data on the effect of consumption of soy products on homocysteine levels. Overall, across studies, there were no discernable differences in effect based on baseline levels, soy protein consumption, soy isoflavone consumption, soy incorporated into diet or as supplement, or population (post-menopausal women, pre-menopausal women, men). Four studies reported greater net effect of soy on homocysteine levels compared to controls. Given the small number of studies no definite

conclusions can be made on the beneficial effect of soy protein consumption on this CVD risk factor.

Table 37. Effect of soy products on homocysteine (μmol/L)

Diet/Supplement	Design	Control	Dose							Change			Net Change				
			mg/day				g/day										
Author Year	Duration	Intervention	Genistein	Daidizein	Glycitein	T. Isoflav	Soy Protein	N	Base value	Value	P within	P btw Soy	Value	P vs Control	Population	Applicability	Quality
Diet	Xover	Dairy															
Jenkins 2002 12145008	4 wk	ISP w/Isoflavones				73	50	41	8.2	*-0.6*		NS[a]	*-0.2*	<0.5[b]	post♀♂	👫	C
		ISP w/Isoflavones				10	52		8.2	*-0.8*			*-0.4*	<0.5[b]			
		Low fat dairy + egg protein							8.0	*-0.4*							
Supplement	Xover	Dairy															
Hermansen 2001	6 wk	ISP w/Isoflavones				>165	50	20	11.2	*+0.4*			*-1.7*	0.006[b]	♀♂ DM	🧍	C
		Casein							10.6	*+2.1*							
Supplement	RCT	Dairy															
Puska[d] 2004	8 wk	ISP				153	41	69/59[e]	10.4	+2.4			+0.6	NS	post♀♂	👫👫	B
		Calcium caseinate						74/73[e]	11.6	+1.9							
Tonstad 2002	16 wk	ISP w/Isoflavones				185	50	31	10.6	*-0.2*		nd	-0.8	0.005[c]	post♀♂	👫	B
		ISP w/Isoflavonessofalvones				111	30	34	10.0	*-0.2*							
		Casein, 50 g						36	10.6	*+0.9*							
		Casein 30 g						29	10.1	*+0.5*							
Puska 2002	6 wk	ISP w/Isoflavones				96	52	24	10.5	-0.3			-1.7	<0.001	post♀♂	🧍	C
		Calcium caseinate						28	9.6	+1.4							

Apparent discrepancies between Within-Cohort changes and Between-Cohort changes are due to rounding errors in estimated Within-Cohort changes compared to reported Between-Cohort changes.

[a] No significant response to treatment high and low isoflavone phases and between sexes
[b] Difference of final values (cross-over study)
[c] Significant for the interaction between treatment and time.
[d] Analyzed on a modified intention-to-treat population and treatment effect estimation for homocysteine by ANCOVA
[e] N: baseline/at 2 weeks of treatment

3.2.11. Endothelial Function

(Table 38)

Endothelial cells in the intima layer of blood vessels play a central role in inhibiting the development of atherosclerosis and its thrombotic consequences. Production of nitric oxide by endothelial cells inhibits monocyte, leukocyte, and platelet adhesion to the vessel wall; decreases permeability to LDL; inhibits smooth muscle cell proliferation; and causes vessel dilation. Endothelial function is determined by measuring the dilation of blood vessels or increased blood flow in response to stimuli that cause endothelial cells to release paracrine factors such as nitric oxide. Patients with risk factors for coronary heart disease as well as those with established coronary heart disease have been found to have impaired vasodilator responses. However there is no evidence that improvements in endothelial function as currently measured results in reduced risk of cardiovascular disease.

The endothelial function of coronary arteries is measured by coronary angiography. The measurement parameter generally used is percent change in coronary artery diameter in response to acetylcholine infusion. Peripheral artery endothelial function is measured either as flow-mediated vasodilation, blood flow rate (or peak flow velocity) in forearm blood vessels including the brachial artery, or as peripheral artery diameter. Endothelial-dependent function is measured in response to a vasodilatory stimulus to the endothelium such as reactive hyperemia after a period of ischemia caused by forearm tourniquet or acetylcholine.

Study Descriptions

Nine RCTs – 5 with a cross-over design – and one cohort study reported the results for peripheral endothelial function of brachial artery.[24,70,76,77,90,94,102,110,118,125] One RCT recruited men and post-menopausal women while the other 8 had only post-menopausal women. The cohort study included only men. The duration of the studies ranged between 6 weeks and 1 year and the studies ranged in size from 18 to 179 subjects. The studies were of poor to moderate quality (1 A, 4 B, 5 C) with generally limited applicability to post-menopausal women; 2 studies also analyzed men. Two studies incorporated the soy products into the diet; the remaining supplemented diets with soy products. Six studies investigated isolated soy protein with isoflavone, one of which also investigated isolated soy protein without isoflavone. The remaining 4 studies investigated pure soy isoflavones.

Overall Effect

Almost all the studies reported either no effect with soy product consumption on endothelial-dependent function or improvements in function, as implied by either increased brachial artery diameter (mm), flow-mediated dilation (% change from basal), flow (mL/min), or decreased peak flow velocity (cm/sec). Only Teede 2001[77] found a statistically significant worsening of endothelial function, as indicated by a net decrease in flow-mediated dilation among men. In contrast, 3 studies reported statistically significant improvements in endothelial function[76,102,125] and the remaining studies generally also found small, non-significant improvements.

Soy Product, Dose, Other Variables

Given the variety of outcome metrics used by different studies and the small number of studies, it is difficult to make cross-study comparisons in regards to different types or doses of soy products investigated. The largest, most statistically significant improvement in endothelial function was reported by Squadrito 2003[125] in a study of pure genistein in post-menopausal women. However, Lissin 2004,[94] the other study with a similar amount of pure soy isoflavones did not find a significant effect.

Only Steinberg 2003[102] directly compared different soy products. Two isolated soy protein products, one with and one without isoflavones, were compared to milk protein. While the soy product with isoflavones resulted in a statistically significant improvement and the soy product without isoflavones did not, the difference between the 2 soy products was small and non-significant.

Teede 2001[77] performed separate sub-analyses of men and post-menopausal women. As noted above, the only finding of a detrimental effect was seen among the men. A small, non-significant improvement was found among the women consuming soy protein with isoflavones.

Summary

Nine randomized trials and 1 cohort study of generally poor to moderate quality and limited applicability investigated the effect of isolated soy protein or pure soy isoflavones on endothelial-dependent function. Overall, limited evidence suggests a possible small improvement in endothelial-dependent function with consumption of soy products by post-menopausal women. However, 1 of 2 studies of men reported a significant worsening of function with soy consumption. There is insufficient evidence regarding different types or doses of soy products to compare their relative effectiveness.

Table 38. Effect of soy products on measures of endothelial function

Diet/Supplement / Author Year	Design / Duration	Control / Intervention	Dose mg/day Genistein	Daidzein	Glycitein	g/day T Isoflav	Soy Protein	N	Outcome (Stimulant)	Unit	Base value	Change Value	Change P within	Net Change[a] P btw Soy	Net Change Value	Net Change P vs Control	Population	Applicability	Quality
Diet	Xover	Dairy																	
Steinberg 2003	6 wk	ISP w/Isoflavones	55	47	5	107	25	24	PFV (RH)	%	nd	+13[b]		NS	-7	0.03[c]	post♀	♂	C
		ISP w/o Isoflavones	1	0.5	0.5	2	24					+15[b]			-5	NS[c]			
		Total milk protein										+20[b]							
Diet	Cohort	No Control																	
Yildirir 2001	6 wk	ISP w/Isoflavones					20	20	BAD (RH)	mm	4.7	*+0.3*	<0.001		--		♂	♂	C
									FMD (RH)	%	8.2	*+4.4*	0.002		--				
		No control group						--											
Supplement	Xover	Dairy																	
Blum 2003 12659466	6 wk	ISP w/Isoflavones				85	25	24	BAD (RH)	mm	nd	3.94[d]			*+0.20*	NS[c]	post♀	♂	C
		Total milk protein										4.13[d]							
		ISP w/Isoflavones				85	25	24	Flow	mL/min	nd	76[d]			-5	NS[c]			
		Total milk protein										81[d]							
Cuevas 2003	8 wk	ISP w/Isoflavones	48	24	8	80	<40	18	FMD (RH)	%	5.3	*+3.9*	<0.03		*+4.3*	<0.03[c]	post♀	♂	B
		Caseinate										*-0.4*	NS						
Supplement	RCT	Dairy																	
Kreijkamp-Kaspers 2005	52 wk	ISP w/Isoflavones	52	41	6		26	88[e]	FMD (RH)	%	4.8	*+0.3*			+0.4	NS	post♀	♂♂	A
		Total milk protein						87[e]			4.4	*0*							
Teede 2001	13 wk	ISP w/Isoflavones	77	38	5	118	40	96[f]	FMD (RH)	%	nd	-3.5[b]			*-3.5*	<0.02	♂	♂♂	C[g]
		Casein									nd	0[b]							
		ISP w/Isoflavones	77	38	5	118	40	83[f]			nd	+0.5[b]			*+1.5*	NS	post♀	♂♂	
		Casein									nd	-1.0[b]							
Supplement	Xover	Placebo																	
Simons 2000	8 wk	Isoflavones				80	0	19	FMD (RH)	%	2.1	*+2*	NS		*+0.8*	NS	post♀	♂	B
		Placebo										*+1.2*	NS						
Nestel 1997	5 wk	Isoflavones	45	35	3	80	0	9	Flow (RH)	%	nd	+88[d]			+0.3	NS[c]	post♀	♂	C
		Placebo										+87[d]							
		Isoflavones	45	35	3	80	0	9	Flow (Ach 37)	%	nd	+87[d]			+2	NS[c]			
		Placebo										+85[d]							

continued

Table 38. Continued

Diet/Supplement Author Year	Design Duration	Control Intervention	Dose (mg/day) Genistein	Daidizein	Glycitein	T Isoflav	Dose (g/day) Soy Protein	N	Outcome (Stimulant)	Unit	Base value	Change Value	Change P within	Net Change[a] P btw Soy	Net Change[a] Value	Net Change[a] P vs Control	Population	Applicability	Quality
Supplement	RCT	Placebo																	
Squadrito 2003	52 wk	Genistein	54				0	27	BAD (RH)	mm	3.5	*+0.5*			*+0.5*	0.02	post♀	♂	B
											3.5	*0*							
									Flow (RH)	mL/dL/min	24	*+11*			*+10*	<0.001			
		Placebo						26			24	*+1*							
		Genistein	54				0	27	BAD (RH)	mm	3.5	*+0.5*			*+0.5*	0.02			
		Placebo						26			3.5	*0*							
Lissin 2004	6 wk	Isoflavones	44	44	2	90	0	20	FMD (RH)	%	1.3	+3.4	NS		*+4*	NS	post♀	♂	B
		Placebo						20			3.8	-0.6	NS						

%, percent change from basal level; Ach 37, Acetylcholine 37 µg/min infusion; BAD, Brachial artery diameter (mm); FMD, Flow-mediated dilation; PFV, Peak flow velocity; RH, Reactive hyperemia.

[a] Or difference between final values, as noted.
[b] Graph
[c] Difference of final values (cross-over study)
[d] Final values. No data on change from start of study.
[e] Intention-to-treat analysis (75 completed soy protocol, 78 completed control protocol)
[f] No data on how many men and how many women completed the study in each arm.
[g] Outcomes reported separately for men and women did not report numbers of subjects.

3.2.12. Systemic arterial compliance

(Table 39)

Coronary arterial perfusion and the distribution of peripheral arterial blood depend on the viscoelastic nature of the aorta. "Arterial compliance" describes the ability of the aorta to distend during the elevated pressure associated with systolic ejection and recoil during the resting diastolic phase of the cardiac cycle Progression atherosclerotic arterial disease leads to a gradual stiffening of the arterial walls. This gradual reduction in aortic viscoelasticity increases cardiac workload and promotes inefficient function. Estrogens have been shown to reduce arterial compliance, dilatation, and blood flow. A beneficial effect of soy is expected to decrease arterial compliance, due to its putative estrogenic effect.

Vascular compliance is calculated as the reciprocal of the slope of the pressure-volume relationship. Techniquest to measure pressure and volume can be evaluated invasively (e.g., arterial catheters) or non-invasively (e.g., echocardiography). The physical units for compliance are typically mL/mm Hg.

Study Descriptions

Three RCTs – 2 with a cross-over design – reported the results for systemic arterial compliance.[24,71,77] All 3 used non-invasive techniques to measure small and large artery or total arterial tree compliance. Two of the studies recruited men and post-menopausal women while the third had only post-menopausal women. The largest included 213 subjects while the other 2 trials had sample sizes of 23 and 21. The duration of the studies ranged between 5 and 13 weeks. The studies were of poor to moderate quality (2 B, 1 C) with generally limited applicability to post-menopausal women and men; 1 study analyzed only post-menopausal women. One study incorporated the soy products into the diet; the remaining supplemented diets with soy products. One study investigated isolated soy protein with isoflavone, one used soymilk and the last study provided pure soy isoflavones.

Overall Effect

All studies reported an improvement in systemic arterial compliance as implied by either the decrease of arterial resistance or the increase in arterial capacitance. Only the smallest trial[24] found a statistically significant effect as indicated by a net increase in systemic arterial compliance in the total arterial tree among post-menopausal women. The remaining studies found small, non-significant improvements.

Soy Product, Dose, Other Variables

Given the small number of studies, it is difficult to make cross-study comparisons in regards to different types or doses of soy products investigated. The only statistically significant improvement in systemic arterial compliance was reported by Nestel 1997[24] in a study of pure isoflavones in post-menopausal women. However, Meyer 2004,[71] the other study with a similar amount of pure soy isoflavones did not find a significant effect.

No study directly compared different soy products. Teede 2001[77] performed separate sub-analyses of men and post-menopausal women. A small, non-significant improvement was found among the men consuming soy protein with isoflavones.

Summary

Three randomized trials of generally poor to moderate quality and limited applicability investigated the effect of soy protein or pure soy isoflavones on systemic arterial compliance. Overall, limited evidence suggests a possible small improvement in systemic arterial compliance with consumption of soy products by men and post-menopausal women. There is insufficient evidence regarding different types or doses of soy products to compare their relative effectiveness.

Table 39. Effect of soy products on measures of systemic arterial compliance

Diet/Supplement	Design	Control	Dose									Change			Net Change[a]				
			mg/day				g/day												
Author Year	Duration	Intervention	Genistein	Daidizein	Glycitein	T Isoflav	Soy Protein	N	Artery Unit	Base value	Value	P within	P btw Soy	Value	P vs Control	Population	Applicability	Quality
Diet	Xover	Dairy																
Meyer 2004	5 wk	Soy milk/ yogurt				80	30	23	Arterial resistance Distal /small artery x 100 mL/mm Hg	5.8	*-0.6*	NS		-0.05	NS[b]	post♀ ♂	↑	B
		Low fat milk/ yogurt									*-0.6*	NS						
		Soy milk/ yogurt				80	30		Arterial capacitance Proximal/ large artery mL/mm Hg	13	*+0.5*	NS		*-0.4*	NS			
		Low fat milk/ yogurt									*+0.9*	NS						
Supplement	RCT	Dairy																
Teede 2001	13 wk	ISP w/Isoflavones	77	38	5	118	40	86	Total arterial tree mL/mm Hg	0.53	+0.04			*+0.03*	NS	post♀ ♂	↑	B
		Casein						93		0.56	+0.01							
		ISP w/Isoflavones	77	38	5	118	40	96[c]		0.54	+0.06			*+0.06*	NS	♂		
		Casein								0.62	0							
		ISP w/Isoflavones	77	38	5	118	40	83[c]		0.52	+0.02			*0*	NS	post♀		
		Casein								0.50	+0.02							
Supplement	Xover	Placebo																
Nestel 1997	5 wk	Isoflavones	45	35	3	80	0	21	Total arterial tree mL/mm Hg	0.67	+0.32	<0.05		*+0.19*	0.01	post♀	↑	C
		Placebo									+0.13	<0.05						

[a] Or difference between final values, as noted
[b] Difference of final values (cross-over study)
[c] No data on how many men and how many women completed the study in each arm.

3.2.13. Oxidized Low Density Lipoprotein

(Table 40)

LDL is normally oxidized to a highly injurious product that results in characteristic endothelial dysfunction in large arteries and resistance vessels. The administration of lipid-soluble antioxidants such as vitamin E or probucol is associated with an increase in the resistance of LDL to oxidative modification. However, trials have not supported the hypothesis that supplementation of vitamin E or probucol in humans reduces cardiovascular risk.

Oxidation of LDL is usually evaluated by studying the kinetics of copper-mediated LDL oxidation products *in vitro*. Typically purified LDL is mixed with copper ions and monitored by means of spectrophotometry for 5 to 6 hours. From the absorbance-over-time curve the following parameters can be estimated: the lag time (expressed in minutes) which is defined as the interval between the initial absorbance and the start of the oxidation phase (start of the propagation phase); the rate of protein-conjugated diene production which is defined as the slope during the oxidation of LDL; the maximal concentration of diene produced during LDL oxidation; and the time of maximal concentration (T max). These parameters can be used to indicate how soy consumption influences the susceptibility of LDL to oxidation.

A beneficial effect of soy on LDL oxidation is expected to decrease all or most of the four parameters above. However, there is little agreement as to which parameter is the best measure of LDL oxidizability. More importantly, it is not clear that any *in vitro* measure of LDL oxidizability truly measures LDL oxidizability in the body or levels of LDL oxidation in atherosclerotic lesions. There is currently no indication that reducing any measure of LDL oxidation is associated with clinical benefit.

Study Descriptions

Eight RCTs with a cross-over design (reported in 9 articles), and one cohort study reported the results for oxidized LDL.[24,49,57,64,68,69,85,126-128] Two RCTs recruited men and women, 4 men and post-menopausal women while 1 had only men, and 1 included only post-menopausal women. The cohort study recruited only post-menopausal women. The sample sizes for the RCTs ranged between 15 and 73. The cohort study had 42 participants. The duration of the studies ranged between 4-12 weeks. The metric used to determine oxidized LDL included ratio of conjugated diene concentration in 1 study, lag time when copper used as oxidative means in 2 studies, conjugated diene concentration in 1 study, and concentration of thiobarbituric acid reactive substances (TBARs) in 2 studies. One RCT reported conjugated diene concentration, and TBARs in 2 publications. There was also an RCT that used both hyperoxide concentration and lag time to evaluate LDL oxidation. Another trial reported lag time, oxidation rate, and maximum diene concentration as well as TBARs. The studies were generally of poor quality (3 B, 6 C) with moderate to good applicability to women and men; 1 study also analyzed men and another one post-menopausal women. Three studies incorporated the soy products into the diet; the remaining supplemented diets with soy products. Four studies investigated isolated soy protein with isoflavone, 3 investigated soymilk, one of which added soy nuts, as well. One study provided tofu, and another one soy flour. The last study investigated pure soy isoflavones.

Overall Effect

Almost all the studies reported either no effect with soy product consumption on oxidation parameters or improvements in oxidized LDL, as implied by the decrease in all or in the majority of the markers measured in each trial. Only Kurowska 1997[69] and Scheiber 2001[128] found a statistically significant worsening of oxidation markers, as indicated by an 11 percent increase in TBARs among men and women, and a net increase in lag time within post-menopausal women, respectively in the 2 studies. In contrast, 7 controlled trials reported statistically significant improvements in oxidized LDL[49,57,64,68,126,127] and the remaining study[24] also found small, non-significant improvements in 3 out of 4 oxidation parameters.

Two additional studies reported findings that are not included in the Summary Table. A randomized cross-over study provided soycreme (10.6% protein, 180 ml of a 1:1 soycreme-water mixture) to patients with cerebral thrombosis.[129] Kanazawa 1995[129] reported as outcomes the X1 and X2 spots, formulated by lipids when developed on thin-layer chromatography and was stained in standing iodine vapor. X1 and X2 spots reflect the lipoprotein peroxidation. Higher percentages of these spots were observed after $CuCl_2$ oxidation in patients not consuming the soycreme compared with those who received soycreme ($P<0.01$ in 24, 48, and 72 hours). Steinberg 2003,[102] which measured lipid oxidation susceptibility by conjugated diene formation, found no significant differences among treatment groups either as absolute values or as the change in lag time from baseline. This study did not report specific data.

Soy Product, Dose, Other Variables

Given the variety of outcome metrics used by different studies and the small number of studies, it is difficult to make cross-study comparisons in regards to different types or doses of soy products investigated. Jenkins 2002[49] reported the largest, most statistically significant improvement in LDL oxidation, as estimated by conjugated diene concentration, in a study of isolated soy protein with isoflavones in the group of post-menopausal women. All studies that reported isoflavone dose, administered higher doses of isoflavones than Jenkins 2002[49] but did not reach an effect. Scheiber 2001,[128] however, mentioned a significant worsening for oxidized LDL.

Only Jenkins 2002[49] directly compared different isoflavone doses. Two isolated soy protein products, one providing 73 mg per day and one 10 mg per day isoflavones, were compared to milk protein. Both isoflavone doses resulted in a statistically significant improvement.

Jenkins 2002[49] also performed separate sub-analyses of men and post-menopausal women. As noted above, the largest significant improvement was seen in post-menopausal women. A smallest, significant improvement was found among the men consuming soy protein with 10 mg per day isoflavones while a similar but non-significant improvement was reported among the men with 73 mg of isoflavones per day.

Summary

Nine randomized trials and 1 cohort study of generally poor quality and moderate to good applicability investigated the effect of soy protein or pure soy isoflavones on LDL oxidation. Overall, evidence suggests a possible improvement in LDL oxidation with consumption of soy products by men or women. However, 1 of 2 studies of men and women found a significant worsening of LDL oxidation with soy consumption. There is insufficient evidence regarding different types or doses of soy products to compare their relative effectiveness.

Table 40. Effect of soy products on measures of oxidized low density lipoprotein

Diet/Supplement	Design	Control	Dose (mg/day)				Dose (g/day)				Change			Net Change[a]				
Author Year	Duration	Intervention	Genistein	Daidzein	Glycitein	T. Isoflav	Soy Protein	N	Outcome (Unit)	Base value	Value	P within	P btw Soy	Value	P vs Control	Population	Applicability	Quality
Diet	Xover	Dairy																
Jenkins 2002	4 wk	ISP w/Isoflavones				73	50	37	CD (pmol/L)	97.9	*-37%*		NS	*-46%*	0.03	post♀ ♂	↑	C
		ISP w/Isoflavones				10	52			82.2	*-25%*			*-34%*				
		Dairy + egg protein								71.3	*+9%*							
		ISP w/Isoflavones				73	50	nd		nd	*-16%*		NS	*-16%*	NS	♂		
		ISP w/Isoflavones				10	52				*-16%*			*-16%*	<0.05			
		Low fat dairy+egg protein									*+1%*							
		ISP w/Isoflavones				73	50	nd		nd	*-20%*		NS	*-55%*	<0.01	post♀		
		ISP w/Isoflavones				10	52				*-18%*			*-53%*	<0.01			
		Low fat dairy+egg protein									*+35%*							
Jenkins [b] 1999 Jenkins [b] 2000 10778882	4 wk	ISP w/Isoflavones	17	34	4	86	33	31[b]	CD (pmol/L)	67	-16%			-18%	<0.001	post♀ ♂	↑	B
		Vegetarian diet								62	+2%							
		ISP w/Isoflavones	17	34	4	86	33		CD:LDL (µmol/mmol)	15.7	-4%			-12%	0.03			
		Vegetarian diet								14.6	+8%							
		ISP w/Isoflavones	17	34	4	86	33		TBARs (µmol/L)	6.08	-1%			+1%	NS			
		Vegetarian diet								6.35	-2%							
Jenkins [b] 2000 10647066	4 wk	ISP w/Isoflavones				168	36	20[b]	CD:LDL (µmol/mmol)	nd	12.9[c]			-8%	0.02[d]	post♀ ♂	↑	C[e]
		Low fat dairy protein									14[c]							
Diet	Xover	Animal diet																
Ashton 2000 11194529	4 wk	Tofu	84	35		120	36	42	Lag time (min)	nd	*49.23*[c]			*-14%*	0.01[d]	♂ post♀	↑	C
		Lean meat									*42.45*[c]							
Diet	Xover	Miscellaneous																
Gardner-Thorpe 2003	6 wk	Soya flour	45	75		120		19	Hydroperoxides (µmol /L)	2.69	*-13%*			-9%	0.009	♂	↑	B
		Wheat flour									*-4%*							
		Soya flour	45	75		120			Lag time (min)	59	*+2%*			0%	NS			
		Wheat flour									*+2%*							
Diet	Cohort	No control																
Scheiber 2001	12 wk	Soy nuts & milk				60		42	Lag time (min)	34.9	+9%	<0.05		--		post♀	↑	C
		No control group						-										
Supplement	Xover	Dairy																
Bricarello 2004	6 wk	Soy milk	50	33	5	87	25	60	TBARs (nmol/mL)	1.82	*-18%*			*-23%*	<0.05	♀♂	↑	C
		Non-fat milk									*+5%*							
Kurowska 1997	4 wk	Soy milk					31	34	TBARs (µmol/mL)	1.35	*+4%*			*+11%*	0.01	♀♂	↑	B
		Milk, 2% fat									*-7%*							
Supplement	Xover	Placebo																
Nestel 1997	5 wk	Isoflavones	45	35	3	80	0	15	Lag time (min)	nd	53.2[c]			-1%	NS[d]	post♀	↑	C
		Placebo									53.5[c]							
		Isoflavones	45	35	3	80	0		Ox Rate (nmol/mg)	nd	14.1[c]			-2%	NS[d]			
		Placebo									14.4[c]							
		Isoflavones	45	35	3	80	0		Max Diene C (nmol/mg)	nd	406[c]			-1%	NS[d]			
		Placebo									409[c]							
		Isoflavones	45	35	3	80	0		TBARs (nmol/mg)	nd	72[c]			+3%	NS[d]			
		Placebo									70[c]							

CD:LDL: Ratio of conjugated dienes (µmol) per mmol LDL; CD: conjugated dienes; TBARs: thiobarbituric acid reactive substances; Ox Rate: oxidation rate; Max Diene C: maximum diene concentration

[a] Or difference between final values, as noted
[b] Jenkins 2000 (UI 10647066) included a subset of subjects from Jenkins 1999 / Jenkins 2000 (UI 10778882), but in a separate study.
[c] Final values (baseline data not reported).
[d] Difference of final values (cross-over study)
[e] In contrast with other outcomes in this article, no baseline CD:LDL value was reported

3.3. Menopausal Symptoms

(Tables 41-45)

A total of 21 trials examine the effects of soy and/or its isoflavones on clinical outcomes of menopausal symptoms (Tables 41-45). Menopausal symptoms usually include vasomotor (e.g., hot flashes and night sweat), psychological (e.g., depression, anxiety, insomnia), and various other symptoms (e.g. palpitations, loss of libido) associated with estrogen deficiency. Vasomotor symptoms are the most common and most studied symptoms of menopause.

Table 41. Summary of studies included for outcomes of menopausal symptoms

Author, Year	Clinical Outcomes – Menopausal Symptoms				Intermediate markers of menopausal symptoms
	Vasomotor symptoms		Psychological symptoms	All other menopausal symptoms	
	Hot Flash	Night Sweat			
Albert, 2002	X		Depression, anxiety, insomnia	Vaginal dryness, bone pain, loss of libido	
Albertazzi, 1998	X				
Balk, 2002	X	X	Depression, insomnia	Urinary discomfort, headache, palpitations, loss of libido	
Burke, 2001	X	X			
Crisafulli, 2004	X				
Dalais, 1998	X				Vaginal cytology maturation
Faure, 2002	X	X			
Han, 2002	X		Insomnia, nervousness, melancholia	Vertigo, weakness, arthralgia and myalgia, headache, palpitation, formication	
Knight, 2001	X		Greene psychological and somatic score		
Kotsopoulos, 2000	X		Irritability, depression, unloved feelings, anxiety, insomnia tiredness	Vaginal dryness, loss of libido, dyspareunia, headaches, joint pain, muscle pain, backache, facial hair, dry skin	
Murkies, 1995	X				Vaginal maturation index
Nikander, 2004	X		Depression, Self-confidence	Menopausal visual analogue scale, work ability index	
Penotti, 2003	X				
Quella, 2000	X				
Russo, 2003	X				
Scambia, 2000	X				Vaginal cytology maturation
Secreto, 2004	Greene vasomotor subscale		Greene psychological subscale	Greene somatic subscale	Occurrence of menstrual flow
St Germain, 2001	X	X	Mood swings	Loss of libido, vaginal dryness, urinary frequency or urgency	
Upmalis, 2000	X	X			Endometrial thickness, vaginal maturation index
Van Patten, 2002	X				
Washburn, 1999	X				

Table 42. Number of women's health studies included with different study designs (and total)

Study Design	Vasomotor Symptoms
Parallel	16
Cross-over	4
Single-Cohort trial	1
Total	**21**

Table 43. Number of women's health studies included within each population and quality category

		Vasomotor Symptoms		
Quality		A	B	C
Population Category	Total			
Post-Menop Women	**17**	1	4	12
Pre-Menop Women	**0**	0	0	0
Peri-Menop Women	**3**	0	2	1
All Women	**1**	0	0	1

Post-Menop = post-menopausal; Pre-Menop = pre-menopausal

Table 44. Number of women's health studies (or study arms) included that used different types of soy products, controls, or soy consumption types (diet versus supplement)

	Vasomotor Symptoms
Soy Product (Study Arms)	
Protein with Isoflavones	11
Protein without Isoflavones	1
Isoflavones	9
Control Types (Study Arms)	
Casein	3
Animal/Usual Diet	0
Placebo	10
Miscellaneous	5
No Non-Soy Control	2
Diet or Supplement (Studies)	
Diet	3
Supplement	18

Table 45. Number of women's health studies that directly compared the effects of different soy product characteristics or study subject characteristics

Comparison Characteristics	Vasomotor Symptoms
Protein with *v* without Isoflavones	2
Different Soy Protein Dosages	0
Different Soy Isoflavone Dosages	2
Different Population Categories	0

Vasomotor Symptoms

(Tables 46-47)

The common vasomotor symptoms associated with menopause include hot flashes (or flushes) and night sweats. The 21 trials that evaluated vasomotor symptoms generally measured frequency and severity of the symptoms using a wide variety of vasomotor symptom scores or indices. These factors make meta-analyses unsuitable and limited the comparisons of results across studies. Furthermore, many of the studies had high withdrawal or dropout rates that were frequently uneven between soy treatment and control arm; this further limits the validity of these clinical trials.

Due to different time intervals for hot flash frequencies and different measurement tools for hot flash scales (sometimes including night sweats), the baseline values are not comparable across studies. In order to gain insight on the effects of soy and/or its isoflavones from this group of variable studies, we first converted the different measurements to a standard unit (percent change from baseline) and, when possible, to the same time interval for hot flash frequencies. A negative percent change in the hot flash scores or frequency indicates a beneficial effect of the treatment, indicating that treatments of soy and/or its isoflavones treatment have net reductions of vasomotor symptoms. Since placebo effects (significant changes within the placebo or control groups) were observed in all studies, a positive net percent change indicates only that treatments of soy and/or its isoflavones were less effective than control in reducing vasomotor symptoms, not that symptoms worsened due to soy treatment.

Hot Flash Frequencies or Scores in Post-Menopausal Women

(Table 46)

Study Descriptions

A total of 17 studies (in 18 articles) reported hot flash frequencies or scroes in post-menopausal women, including 3 soy diet trials and 14 soy supplement trials.[46,47,66,91,130-143] Twelve of the 17 studies are of poor quality (grade C); only 2 are high-quality studies (grade A); and the remaining studies are of medium quality (grade B).

Two RCTs and 1 cross-over study compared soy diet with different types of grains (wheat or corn) as controls. The methodological quality of these 3 studies was poor. No consistent effect was found in this group of studies.

Four trials examined the effects of soy protein supplements with isoflavones on vasomotor symptoms. One (Van Patten 2002) evaluated post-menopausal women with breast cancer.[132] The other trials compared soy to casein in healthy post-menopausal women. All studies reported that soy supplements decreased hot flash scores or frequency. However, in the study of women with breast cancer the control group had a statistically non-significant greater decrease in frequency, and only in the study by Albertazzi 1998,[133] was the decreas statistically significantly greater than control. Of note though, in Kotsopoulos 2000, 20% of the women had no hot flash symptoms at baseline, lowering the likelihood of finding a benefit.[135] In addition, all studies had small sample sizes and/or high dropout rates.

Nine trials (2 cross-over trials and 7 RCTs) examined the effects of soy isoflavones (without soy protein) on vasomotor symptoms. The 2 cross-over trials showed that placebo decreased hot flash symptoms as much as isoflavones. Six of the 7 RCTs found significant

effects of soy isoflavones in reducing vasomotor symptoms in post-menopausal women. In contrast, Penotti 2003 found that both soy isoflavone treatment as well as the placebo decreased the same numbers of hot flashes per month.[142] However, the initial hot flash frequency in this study was lower compared to the other 6 RCTs of isoflavone supplements.

One non-controlled trial by Albert 2002 showed that 4-month soy isoflavone supplementation decreased the hot flash score significantly in 146 post-menopausal women who suffered at least 6 moderate or severe daily hot flashes during the 15 days prior to the study.[143] Since statistically significant decreases in vasomotor symptoms were common in the control arms of other studies, it cannot be concluded that this study supports a benefit of soy isoflavones.

Summary

Overall, the effects of soy protein and/or its isoflavones are inconsistent across studies. Every trial found a decrease in hot flash frequencies or scores in the treatment groups, as well as in the control or placebo groups. This makes the results difficult to be interpreted. Across studies, 6 (35%) studies showed no or worsening effects and 11 (65%) studies showed soy protein and/or its isoflavones non-significantly or significantly decreased hot flash frequencies or scores in post-menopausal woemen. The evidence of a benefit was stronger among the RCTs of isoflavone supplements, which mostly showed positive results – the net reduction in weekly hot flash frequency ranged from 7% to 40%. However, these trials are mostly rated as poor quality due to high dropout rates.

Hot Flash Frequencies or Scores in Peri-Menopausal Women and Women who had Breast Cancer Therapies

(Table 47)

Study Descriptions

Four studies reported hot flash frequencies or scores in non-post-menopausal women,[23,117,144,145] including 3 studies in peri-menopausal women and 1 study in women who were on breast cancer therapies. Two were cross-over trials and 2 RCTs. Of these, 3 trials compared soy protein and/or its isoflavones to a placebo or casein control. No significant effect of soy protein and/or its isoflavones on vasomotor symptoms was found in peri-menopausal women or women who had breast cancer therapies, although 1 study (St Germain 2001) found that women who received isolated soy protein without isoflavones had no change in the weekly hot flash frequency while those who received soy protein with isoflavones or placebo had decreased frequency.[145]

Burke 2001 compared the effects of high and medium dose isolated soy protein with isoflavones to isolated soy protein without isoflavones on vasomotor symptoms in peri-menopausal women.[146] It found that all 3 treatments significantly decreased the daily reported vasomotor symptoms (hot flashes and night sweats), but there was no significant difference of the effects among the 3 treatments and there was no non-soy control group.

Summary

There are only 4 studies that evaluated the effect of soy consumption on menopausal symptoms in peri-menopausal women or those receiveing breast cancer therapy. Among these studies there is no evidence that soy consumption is better than control to reduce menopausal symptoms. The range of changes in symptoms among women consuming soy was large, from –77% to +23%.

Table 46. Effects of soy products on vasomotor symptoms (e.g. hot flash frequencies or scores) in post-menopausal women

Diet Supplement / Author Year	Design / Duration	Control / Intervention	Dose mg/day Genistein	Daidizein	Glycitein	T. Isoflav	g/day Soy Protein	N	Base value	Unit	% Change Value	% Change P within	% Change P btw Soy	Net % Change Value	Net % Change P vs Control	Base Prev (Hot Flash)	Applicability	Quality
Diet	Xover	Miscellaneous																
Dalais 1998	12 wk	Soy bread				53		44	nd	Frequency per day	*-23* [a]	NS		*+28*		100%	🚺🚺	C
		Wheat bread									-51	<0.01						
Diet	RCT	Miscellaneous																
Murkies 1995	12 wk	Soy flour		40 g of flour per day				23	42	Frequency per week [n]	*-42*	<0.001		*-17*	NS	100%	🚺	C
		Wheat flour						24	37.1		*-25*	<0.001						
Balk 2002	6 mo	Soy cereal				~100		13/7 [b]	1.31	Frequency per week	*-33*	0.06		*+28*		nd	🚺	C
		Corn cereal						14/12 [b]	1.28		*-61*	0.01						
Supplement	RCT	Miscellaneous																
Van Patten, 2002	4 wk	Soy beverage				90[q]		59	4.7	Frequency per week	-26	<0.05		*+9*	NS	100%	🚺🚺🚺 BrCA	C
		Rice beverage						64	5.2		-35	<0.05						
Supplement	RCT	Casein																
Albertazzi 1998; 1999	12 wk	ISP w/Isoflavones	40	28		76	40	40	11.4[c]	Frequency per week	-44 [r]	<0.05		*-13*	<0.01	100%	🚺🚺🚺	B
		Casein						39	10.9[c]		*-31* [r]	<0.05						
Kotsopoulos 2000	3 mo	ISP w/Isoflavones				96.3[d]	56[d]	31	0.82	Hot flash score [m]	*-6*	NS		*-4*		80%	🚺	C
		Casein						41	0.85		*-2*	NS						
Knight 2001	12 wk	ISP w/Isoflavones	49	25	3	77	35	9	*4.18*	Frequency per week[e]	-43			*-23*	NS	nd	🚺	C
		Casein						11	*4.68*		-20							
Supplement	Xover	Placebo																
Russo 2003	3 mo	Isoflavones				32	0	47	nd	Overall no improvement rate	*-17* [f]	<0.05		*+5*		100%	🚺🚺	B
		Placebo									*-22* [f]	<0.05						
Nikander 2004	3 mo	Isoflavones	7	41	66	114	0	28	2.0	Hot flash score [c]	*-10*	NS		*+4*	NS	100%	🚺 BrCA	B
		Placebo							2.1		*-14*	0.006						
Supplement	RCT	Placebo																
Secreto 2004	3 mo	Isoflavones	12	40	28	80	0	59	4	Vasomotor score [g]	25% no improve [g]			*-6*	<0.05	nd	🚺🚺	B
		Placebo						58	4		31% no improve [g]							
		Isoflavones + melatonin	12	40	28	80	0	61	4		38% no improve [g]			*-1*	NS			
		Melatonin						54	4		39% no improve [g]							
Upmalis 2000	12 wk	Isoflavones		50 [h]			0	59	56.7	Frequency per week [n]	-26 [a]	<0.05		*-7*	0.008 [p]	100%	🚺	C
		Placebo						63	63.7		-19 [a]	<0.05						

continued

Table 46. Continued

Diet Supplement / Author Year	Design / Duration	Control / Intervention	Dose mg/day Genistein	Daidizein	Glycitein	T. Isoflav	Dose g/day Soy Protein	N	Base value	Unit	% Change Value	% Change P within	% Change P btw Soy	Net % Change Value	Net % Change P vs Control	Base Prev (Hot Flash)	Applicability	Quality
Supplement	RCT	Placebo																
Han 2002	4 mo	Isoflavones	70	19	11	100	0	40	11.3	Hot flash score [c]	-27	<0.01		*-26*	<0.01	nd	♀♀♀	A
		Placebo						40	63.7		-1	NS						
Faure 2002	16 wk	Isoflavones				17.5	0	39/32 [b]	10.1	Frequency per week	-61			*-40*	0.01	100%	♀♀	C
		Placebo						35/22 [b]	9.4		-21							
Crisafulli 2004	1 yr	Genistein	54				0	<30 [i]	4.6	Hot flash score [o]	*-50* [a]			-24	<0.01	100%	♀	C
		Placebo						<30 [i]	4.7		*-30* [a]							
Penotti 2003	6 mo	Isoflavones	11	36	25	76	0	28/22 [b]	2.48	Frequency per week [j]	*-54*			*0*	NS	nd	♀	C
		Placebo						34/27 [b]	2.15		*-54*							
Scambia 2000	6 wk	Isoflavones				50	0	20	27	Frequency per week	*-45* [a]			*-21*	<0.01	nd	♀	C
		Lactose						19	33		*-24* [a]							
Supplement	NRCT	No Control																
Albert 2002	4 mo	Isoflavones				35 [k]	0	146	0.83	Hot flash score [l]	-56	<0.003	--	--		100%	♀♀♀	C
		No control						--										

Due to different time intervals for hot flash frequencies and different measurement tools for hot flash scales (sometimes including night sweats), the baseline values are not comparable across studies. Negative net % change indicates that soy and/or isoflavones treatments have net reductions of vasomotor symptoms . Base Prev (Hot Flash) = baseline prevalence of hot flash in the study population. BrCA = breast cancer

[a] Values were estimated from graph
[b] Baseline / final number of subjects
[c] Kupperman index
[d] Derived from 2.11 mg total isoflavones (aglycones and glycosides) per g protein. The amount of aglycone isoflavones was then derived from 1.72 mg alycone isoflavones/g protein.
[e] Derived from the frequency over the 12-week trial
[f] Although a cross-over trial, the data were analyzed descriptively in the study. The percent change for both treatment arms was calculated as follows: (# subjects reported no improvement after soy treatment – # reporting no improvement after placebo treatment) / (# reported no improvement after soy treatment). Dropouts excluded from analyses. This analysis does not consider time effect (i.e. the order of getting treatments).
[g] Greene vasomotor subscale. The change is percent subjects who reported any improvement of vasomotor symptoms (only 2 items). In order to have consistent effect expression as other studies, the numbers in percent change cells are percent of subjects who reported no improvement of vasomotor symptoms.
[h] 50 mg genistein and daidzein
[i] Study population is same as Morabito, 2002. The study only analyzed participants who had at least "5 hot flashes (including night sweats)" but numbers were not reported.
[j] Derived from the number of hot flashes per month
[k] 5% diadzin, 3% glycitin; 1.5% genistin
[l] Hot flash score 0-4 (the higher score, the more frequent the hot flash symptoms)
[m] Scale from 0-3 (the higher score, the worse hot flash symptoms)
[n] Derived from the numbers of hot flashes per day
[o] Hot flash (including night sweat) score incorporates both the number and severity of hot flashes. No further explanation is found in the study.

[p] Repeated measures analysis showed a statistically significant (*P*=0.03) reduction in hot flash frequency over the first 6 weeks in the soy isoflavones arm compared with the placebo, but the result was marginally significant (*P*=0.08) over the 12-week study.

[q] Glucosides
[r] Intention-to-treat data

Table 47. Effects of soy products on vasomotor symptoms (e.g. hot flash frequencies or scores) in peri-menopausal women

Diet /Supplement	Design	Control	Dose					N	Base value	Unit	% Change			Net % Change		Population	Base Prev (Hot Flash)	Applicability	Quality
			mg/day				g/day												
Author Year	Duration	Intervention	Genistein	Daidizein	Glycitein	T. Isoflav	Soy Protein				Value	P within	P btw Soy	Value	P vs Control				
Supplement	Xover	Placebo																	
Quella 2000	4 wk	Isoflavones	60~68	60~68	15~30	150	0	177/ 149[b]	12	Hot flash score [c]	*-30* [a]			*+2*	NS	♀ BrCA	100%	🚹🚹	C
		Placebo							13		*-32* [a]								
Washburn 1999	6 wk	ISP w/Isoflavones once daily				34	14	42	nd	Frequency per week	23 [d]		NS	+2 [d]	NS	peri♀	100%	🚹🚹🚹	C
		ISP w/Isoflavones twice daily				34	14				22 [d]			+1 [d]	NS				
		Carbohydrates									21 [d]								
Supplement	RCT	Miscellaneous																	
St Germain 2001	24 wk	ISP w/Isoflavones				80	40	24	36	Frequency per week	*-50*		nd	*-3*	NS	peri♀	100%	🚹🚹🚹	B
		ISP w/o Isoflavones				4.4	40	24	36.5		*0*			*+47*	NS				
		Wheat protein						21	32		*-47*								
Supplement	RCT	No Control																	
Burke 2001	2 yr	ISP w/Isoflavones				58	25	65	22.4	Frequency per week [e]	*-59*	<0.0001	NS	--		peri♀	96.9%	🚹🚹	B
		ISP w/Isoflavones				42	25	76	18.2		*-42*	<0.0001		--			94.7%		
		ISP w/o Isoflavones				≤4	25	70	24.5		*-77*	<0.0001		--			98.6%		
		No control						--											

BrCA = breast cancer women who were suffering from hot flashes, as defined by their occurrence of> 14 times per week and of such severity to warrant intervention (tamoxifen or raloxifene therapy was allowed). Base Prev (Hot Flash) = baseline prevalence of hot flash in the study population.

[a] Values were estimated from graph
[b] Baseline / final number of subjects
[c] Daily frequency x severity
[d] Data are not % change but final hot flash frequency and calculated net change. No data are found on baseline frequency.
[e] Derived from vasomotor symptoms (hot flash and night sweat) reported per day

3.4. Endocrine Function

(Tables 48-50)

Because of the structural similarity of soy isoflavones to estrogens, it has been suggested that these isoflavones might act as either an agonist or antagonist of estrogen. Several hypotheses have been developed for isoflavones that may have a potential effect on estrogens and their metabolites as well as on other hormones that interfere with estrogen metabolism and pathways of estrogen action. However, it should not be assumed that such effects based on biologically plausible mechanisms of action are also correlated to clinical consequences. Interpretations of soy-related effects on endocrine markers must equally be treated with caution.

Estrogen levels are different between men and women and they are also different between pre-menopausal and post-menopausal women. Therefore, a potential effect of soy isoflavones might be of different clinical importance according to gender and age. To avoid any misinterpretation, endocrine results have been analyzed separately for men, pre-menopausal, and post-menopausal women.

Menstrual cycle length is the number of days from the start of one menstrual bleeding period to the start of the next bleeding period. Normal menstrual cycles require a normal endocrine environment. This endogeous hormonal environment may play a role throughout a woman's life in determining her long-term risk of developing chronic disease[78,147-149]. In addition, a woman's menstrual cycle is an important indicator of her reproductive health.

Forty-seven papers included 50 trials and reported a large number of endocrine outcomes as primary or secondary endpoints (Table 48). In consultation with the TEP, we focused on the most clinically relevant sex hormones – testosterone, follicle stimulating hormone (FSH), and total estradiol (E2) – and thyroid stimulating hormone (TSH). Eleven studies in 10 articles also evaluated menstrual cycle length. All endocrine-related studies are summarized in Tables 49-50.

Table 48. Endocrine functions evaluated in soy studies (not including studies of menstrual cycle length)

Author Year	Testosterone	FSH	Estradiol	TSH	LH	Estrone	Estrone sulfate	Progesterone	Prolactin	Androstenedione	DHEA/DHEAS	Other Sex Hormone	2-hydroxyestrone	16-alpha-hydroxyestrone	Other U Sex Hormone	SHBG	T3	T4	TBG	PTH	Cortisol	IGF-1	Other Endocrine
Duncan 1999 10522983	x post	x	x	x	x	x	x		x	x	x					x	x	x	x		x		
Scambia 2000		x nd			x				x											x			
Upmalis 2000		x																					
Lu 2000		x nd	x nd		x			x															
Xu 2000													x	x	x								
Watanabe 2000			x																				
Mackey - Study 1 2000 (post-menop)		x nd		x nd	x											x							
Mackey - Study 2 2000 (men)	x nd	x nd		x nd	x					x	x					x							
Gardner 2001		x nd	x nd			x				x													
Nagata 2001	x		x men			x										x							
Stroescu 2001	x pre		x					x	x						x		x	x					
Knight 2001		x														x			x				
Teede 2001	x	x			x																		
Scheiber 2001		x	x																				
Persky 2002		x	x	x		x	x				x	x	x	x		x	x	x			x		x
Han 2002		x	x		x																		
Kumar 2002			x			x										x							
Swain 2002		x nd	x nd			x																	
Khalil 2002																						x	
Jayagopal 2002	x post	x		x	x					x	x					x	x	x					
Morabito 2002			x																	x			
Brown 2002	x pre	x	x nd		x	x	x	x	x	x	x		x	x		x					x		
Gardner-Thorpe 2003	x		x men			x						x				x							
Arjmandi 2003			x																			x	
Squadrito 2003			x																				
Nikander 2003		x	x		x											x							
Cuevas 2003		x																					

continued

Table 48. Continued.

Author Year	Testosterone	FSH	Estradiol	TSH	LH	Estrone	Estrone sulfate	Progesterone	Prolactin	Androstenedione	DHEA/DHEAS	Other Sex Hormone	2-hydroxyestrone	16-alpha-hydroxyestrone	Other U Sex Hormone	SHBG	T3	T4	TBG	PTH	Cortisol	IGF-1	Other Endocrine
Chiechi 2003		x	x																				
Cassidy 1995 Study 3		x	x		x			x							x	x							
Cassidy 1995 Study 4		x	X		x			x								x							
Murkies 1995		x																					
Cassidy 1994	x pre	x	x					x							x	x							
Nagata 1998			x			x										x							
Duncan 1999 9920082	x pre	x	x	x nd	x	x	x	x	x	x	x					x	x	x	x		x		
Ham 1993				x													x	x					
Lu 1996			x nd					x			x												
Wu 2000			x nd					x								x							
Hsu 2001			x																				
Foth 2003	x post	x	x		x				x		x												
Uesugi 2003		x																					
Martini 1999			x nd			x		x	x		x	x			x	x							
Adams 2003																						x	
Bruce 2003				x																			
Mitchell 2001	x	x	x men		x																		
Baird 1995		x			x											x							
Petrakis 1996			x					x	x							x							
Maskarinec 2004			x			x		x			x					x							
Lu 2001		x	x		x			x								x							
Habito 2000	x		x men							x	x					x							x
Lenn 2002																					x		

nd: no data; pre: pre-menopausal women; post: post-menopausal women

Summary tables do not include studies that measured testosterone in women (pre or post), or estradiol in men; also studies with “nd” have not been analyzed in the summary tables

Other Sex Hormone: SHBG-bound estradiol (%); Dihydrotestosterone; Ratio: Progesterone/Estradiol
Other Urinary Sex Hormone: estrogens & estrogen metabolites; 17-ketosteroids metabolites of androgenic steroids; urinary LH; ratio: 2-OH-estrone/ 16-a-OH-estrone
Other endocrine outcomes: free thyroxine index (FTI); free androgen index; ratio: testosterone/estradiol.

Table 49. Number of endocrine studies included with different study designs (and total)

Study Design	Endocrine Trials [a]	Menstrual Cycle Length
Parallel	21	7
Cross-over	8	2
Single-cohort trial	10	2
Total	**39**	**11**

[a] Based on studies that have been included in the following tables: 51-56, 58

Table 50. Number of endocrine studies (or study arms) included that used different types of soy products, controls, or soy consumption types (diet versus supplement)

	Endocrine Trials [a]	Menstrual Cycle Length
Soy Product (Study Arms)		
Protein with Isoflavones	27	12
Protein without Isoflavones	3	1
Isoflavones	15	1
Control Types (Study Arms)		
Dairy	5	3
Animal/Usual Diet	6	4
Placebo	13	0
Miscellaneous	3	0
No Non-Soy Control	12	1
Diet or Supplement (Studies)		
Diet	14	8
Supplement	25	4

[a] Based on studies that have been included in the following tables: 51-56, 58

3.4.1. Testosterone

(Table 51)

Higher testosterone level is considered a potential risk factor for prostate cancer by the National Cancer Institute (NCI) (www.nci.nih.gov/cancertopics/pdq/prevention/prostate/). A beneficial effect of soy on risk for prostate cancer is expected to decrease testosterone levels. The National Guideline Clearinghouse also has published guidelines that recommend testosterone should be measured in males as part of the initial evaluation for infertility (www.guideline.gov/summary/summary.aspx?doc_id=2924). Low testosterone levels have been related with clinical conditions that cause male infertility. A beneficial effect of soy on male infertility is expected to increase testosterone levels.

Study Descriptions

Three RCTs – one with a cross-over design - and 2 cohort studies reported the results for testosterone levels in healthy males as an outcome. [77,85,150-152] An additional study reported non-significant effect of soy in healthy male individuals but it did not provide specific results.[88] The 3 RCTs recruited a ramge between 15 and 96 participants in the soy arm. The cohort studies enrolled 19 and 15 men respectively. The duration of the studies ranged between 4 and 13.5 weeks. The studies were of poor quality (C) with generally limited applicability because of the small number of participants. Two studies incorporated the soy products into the diet; the remaining supplemented diets with soy products. One study investigated isolated soy protein with isoflavone, one study used soy flour, one trial provided soy milk, another trial used tofu, and the last study provided pure soy isoflavones.

Overall Effect

Four out of the 5 studies found a decrease in the risk of prostate cancer as implied by the decrease in testosterone levels. However, this limited evidence showed no significant effect.

Soy Product, Dose, Other Variables

Given the small number of studies, it is difficult to make cross-study comparisons in regards to different types or doses of soy products investigated. No study directly compared different soy products.

Summary

Three randomized trial and 2 cohort studies of generally poor quality and limited applicability investigated the effect of soy protein or pure soy isoflavones on testosterone levels in healthy males. The limited evidence suggests a possible trend to lower risk for prostate cancer, with consumption of soy products by men. There is insufficient evidence regarding different types or doses of soy products to compare their relative effectiveness.

Table 51. Effect of soy products on testosterone (nmol/L) in men

Diet /Supplement Author Year	Design Duration	Control Intervention	Dose (mg/day) Genistein	Daidizein	Glycitein	T. Isoflav	Dose (g/day) Soy Protein	N	Base value	Change Value	Change P within	Change P btw Soy	Net Change Value	Net Change P vs Control	Population	Applicability	Quality
Diet	Xover	Miscellaneous															
Habito 2001	4 wk	Tofu [a]						15	15.1	*+0.4*	NS		+0.1	NS	♂	II	C[a]
		Animal diet								*+0.3*	NS						
Diet	Cohort[b]	No control[b]															
Gardner-Thorpe 2003	6 wk	Soy flour	45	75		120		19	19.3	*-1.1*	NS		nd	NS	♂		C [b]
		Wheat flour[b]								nd	NS						
Supplement	RCT	Casein															
Teede 2001	13.5 wk	ISP w/Isoflavones	77	38	5	118	40	96[c]	16.8	*-1.5*	NS		*-0.5*		♂		C [c]
		Casein							15.8	*-1*	NS						
Nagata 2001	8 wk	Soy milk	2.4	2.4		4.8	26.3	17	16.3	*-2.2*	NS		*-1.8*	NS	♂		C
		Usual diet						17	15.6	*-0.4*	NS						
Supplement	Cohort	No control															
Mitchell 2001	8 wk	Isoflavones				40	0	15	30.25	*-3.9*	NS		--		♂		C
		No control group						--									

[a] 150g of tofu; no other ingredient is quantified

[b] Overall study is a randomized cross-over trial; however, testosterone data reported only for soy cohort (in contrast with other outcomes in this article).

[c] In contrast with other outcomes in this article, no data on how many men completed the study in each arm.

3.4.2. Follicle stimulating hormone (FSH)

(Tables 52-54)

The National Guideline Clearinghouse has published guidelines that recommend FSH should be measured in males and females as part of the initial evaluation for infertility (www.guideline.gov/summary/summary.aspx?doc_id=2924; www.guideline.gov/summary/summary.aspx?doc_id=4742&nbr=3435). Marked elevation of serum FSH in men is clearly indicative of an abnormality in spermatogenesis. A beneficial effect of soy on male infertility is expected to decrease FSH levels. Among women, FSH levels greater than 10 mlU/mL are associated with an extremely low pregnancy rate. A beneficial effect of soy on female infertility is expected to decrease FSH levels. FSH in pre-menopausal women is evaluated during the follicular phase of the menstrual cycle. Although FSH level in post-menopausal women generally is not considered of clinical importance, this report also includes the results of studies on post-menopausal women.

Study Descriptions

One RCT and 1 cohort study reported FSH as an outcome in men (Table 52).[77,152] The soy arm in the RCT included 55 men and the cohort study recruited 15 men. The RCT lasted for 12 weeks while the cohort study lasted for 8 weeks. The studies were of poor quality (C) with generally limited applicability because of the small number of participants. Both studies supplemented diets with soy products. One study investigated isolated soy protein with isoflavone, and the other study provided pure soy isoflavones.

Two RCTs including 1 with a cross-over design, and 4 cohort studies (the 3 of them by a single set of researchers were published in 2 articles) reported FSH levels during the follicular phase of the menstrual cycle in pre-menopausal women as an outcome (Table 53).[153-157] The RCTs had 14 and 17 participants in the soy arm while the 4 cohorts reported a sample size of 5 to 9 participants. The duration of the RCTs was 13.5 to 48 weeks. Three of the cohort studies lasted for 2 menstrual cycles while the fourth for 1 menstrual cycle. The studies were generally of poor quality (1 B score, 5 C) with generally limited applicability because of the small number of participants. Three studies incorporated the soy products into the diet; the remaining supplemented diets with soy products. Three of the cohort studies and one of the RCTs investigated isolated soy protein with isoflavone, the fourth cohort used isoflavone-free soy milk while the other RCT provided pure soy isoflavones.

Fourteen RCTs including 4 with cross-over design and 2 cohort studies reported FSH levels in post-menopausal women as an outcome (Table 54).[47,66,76,77,84,91,93,97,123,128,136,158-162] The RCTs recruited 9 to 66 participants in the soy arm while the cohort studies reported sample sizes of 42 and 16 participants. The duration of the RCTs ranged between 4 and 24 weeks. The cohort studies lasted 12 and 24 weeks. The studies were of poor to moderate quality (1 A, 9 B, 6 C) with generally limited applicability to post-menopausal women. Six studies incorporated the soy products into the diet; the remaining supplemented diets with soy products. Eight studies investigated isolated soy protein with isoflavone, one study used soy nuts and milk, one study provided soy flour, and another soy germ capsules. The remaining 5 studies investigated pure soy isoflavones.

Overall Effect

Teede 2001, in the only RCT of effect on FSH in men (Table 52), reported a increase.[77] Mitchell 2001, in the cohort study, noted a very small decrease.[152] None of the effects were statistically significant.

Among pre-menopausal women (Table 53), the only trial with a non-soy control (Maskarinec 2002[155]) found a non-significant relative decrease with soy (although FSH rose in both arms of the study). Only the 1994 cohort study by Cassidy[153] reported a significant (and large) decrease in FSH. Duncan 1999[156] found no difference in effect between 2 different formulations of soy product with different isoflavone contents. There was one more trial, which reported that daily consumption of soy milk had no effect on FSH levels without providing any specific results.[163]

None of the trials among post-menopausal women (Table 54) found a significant difference in effect on FSH between soy and non-soy interventions, or between different soy interventions. There was a wide range of net effects, between –6.4 and +11.9 IU/L.

There were 6 more trials in 5 publications[46,81,98,163,164] that reported FSH level as outcome without providing with specific results. No significant effect is shown in any of these studies.

Soy Product, Dose, Other Variables

For men and pre-menopausal women, given the small number of studies, it is difficult to make cross-study comparisons in regards to different types or doses of soy products investigated. Only Duncan 1999,[156] in pre-menopausal women (Table 53), directly compared different soy products. Two isolated soy protein products, one providing 128 mg per day and one 64 mg per day isoflavones, were compared to each other. No significant change was reported between the 2 arms.

For post-menopausal women (Table 54), the only statistically significant decrease in FSH was reported within the soy arm by Han 2002[91] in a study of pure isoflavones. This decrease was not significant when compared to the controls. However, no other study with a similar or higher amount of pure soy isoflavones found any significant effect.

Persky 2002[160] (Table 54) and Duncan 1999[161] (Table 53) directly compared different isoflavone doses among post-menopausal women. For Persky 2002,[160] 2 isolated soy protein products, one providing 72 mg per day and one 43 mg per day isoflavones, were compared to milk protein. The higher isoflavone dose resulted in a non-significant increase in FSH level while the lower dose resulted in non-significant decrease. In Duncan 1999,[161] 2 isolated soy protein products, one providing 132 mg per day and one 65 mg per day isoflavones, were compared to each other. The soy product with lower isoflavones resulted in a statistically significant decrease but the soy product with higher isoflavones did not. However, none of the 2 trials provided information whether the differences between the 2 soy products were significant.

Summary

One RCT and one cohort study, both of poor quality and limited applicability, investigated the effect of isolated soy protein or pure soy isoflavones on FSH levels among males. Overall, evidence is conflicting on the effect on FSH of soy product consumption by men. Additionally, there is insufficient evidence regarding different types or doses of soy products to compare their relative effectiveness.

Two RCTs and 4 cohort studies of generally poor quality and limited applicability investigated the effect of isolated soy protein or pure soy isoflavones on FSH levels among pre-menopausal women. Overall, evidence is conflicting on the effect on FSH of soy product

consumption by pre-menopausal women. Additionally, there is insufficient evidence regarding different types or doses of soy products to compare their relative effectiveness.

Fourteen RCTs and 2 cohort studies of generally poor to moderate quality and limited applicability investigated the effect of isolated soy protein or pure soy isoflavones on FSH levels among post-menopausal women. Overall, evidence is conflicting on the effect on FSH levels of soy consumption by post-menopausal women. Additionally, there is insufficient evidence regarding different types or doses of soy products to compare their relative effectiveness.

Table 52. Effect of soy products on FSH (IU/L) in men

Diet/Supplement	Design	Control	Dose							Change			Net Change				
			mg/day				g/day										
Author Year	Duration	Intervention	Genistein	Daidizein	Glycitein	T. Isoflav	Soy Protein	N	Base value	Value	P within	P btw Soy	Value	P vs Control	Population	Applicability	Quality
Supplement	RCT	Casein															
Teede 2001	12 wk	ISP w/Isoflavones	77	38	5	118	40	96[a]	11.1	+2.7	NS		-2		♂	👫	C[a]
		Casein							9.2	+4.7	NS						
Supplement	Cohort	No control															
Mitchell 2001	8 wk	Isoflavones				40	0	15	4.44	-0.04	NS		--		♂	🚹	C
		No control group						--									

[a] In contrast with other outcomes in this article, no data on how many men completed the study in each arm.

Table 53. Effect of soy products on FSH (IU/L) in pre-menopausal women

Diet/Supplement	Design	Control	Dose								Change			Net Change		Population	Applicability	Quality
			mg/day				g/day											
Author Year	Duration	Intervention	Genistein	Daidizein	Glycitein	T. Isoflav	Soy Protein	N	Base value	Value	P within	P btw Soy	Value	P vs Control			
Diet	**Cohort**	**No Control**																
Cassidy 1994[a]	~4 wk	ISP w/Isoflavones	20	25			60	6	7.8	*-6.8*	<0.01		--		pre♀	♂	C
		No control group																
Cassidy 1995 (Study 4)[a]	~4 wk	ISP w/o Isoflavones						6	4.6	*0*	NS		--		pre♀	♂	C
		No control group																
Cassidy 1995 (Study 3)[a]	~4 wk	ISP w/Isoflavones						5	4.9	*-0.7*	NS		--		pre♀	♂	C
		No control group																
Supplement	**RCT**	**Placebo**																
Maskarinec 2002	48 wk	Isoflavones				74	0	17	3.2	*+0.6*			*-0.82*	NS	pre♀	♂	B
		Maltodextrin						17	4.1	*+1.3*								
Supplement	**Xover**	**No Control**																
Duncan 1999 9920082	13.5 wk	ISP w/Isoflavones				128		14	nd	*4.32*[b]		NS	--		pre♀	♂	C
		ISP w/Isoflavones				64				*4.31*[b]			--					
		No control group						--										
Supplement	**Cohort**	**No Control**																
Lu 2001	~4 wk	Soy milk w/o Isoflavones					37.9	9	2.7	*-0.2*	NS		--		pre♀	♂	C
		No control group						--										

[a] In the paper of Cassidy 1995, 4 cohort studies are included (S1-S4): the first has also been published as Cassidy 1994 (also reported in the table); the 2nd has been excluded because of inadequate sample size (< 5 women); the 3rd and 4th are reported in the table as Cassidy 1995 (Study 3) and Cassidy 1995 (Study 4) respectively

[b] Only final values are reported in the paper

Table 54. Effect of soy products on FSH (IU/L) in post-menopausal women.

Author Year	Diet/Supplement / Design / Duration	Control / Intervention	Dose mg/day Genistein	Daidizein	Glycitein	T. Isoflav	g/day SProtein	N	Base value	Change Value	P within	P btw Soy	Net Change Value	P vs Control	Population	Applicability	Quality
Diet	**Xover**	**Dairy**															
Cuevas 2003	8 wk	ISP w/Isoflavones	48	24	8	80	<40	18	56.5	*+2.1*	NS		*-1.8*	NS	post♀	♀	B
		Caseinate								*+3.9*	NS						
Diet	**RCT**	**Animal/Usual**															
Baird 1995	4 wk	ISP w/Isoflavones				165	38	66	61.1	*-2.7*			*-0.9*	NS	post♀	♀♀	B
		Usual diet						25	63.4	*-1.8*							
Chiechi 2003	24 wk	ISP w/Isoflavones	27	19	1	47		53	60.9	*+0.9*			*+1.6*	NS	post♀	♀♀	C
		Usual diet						58	59.1	*-0.7*							
Diet	**RCT**	**Miscellaneous**															
Murkies 1995	12 wk	Soy flour[a]						23	84.52	-1.35	NS		*+6.74*	NS	post♀	♀	B
		Wheat flour						24	82.93	-8.09	<0.05						
Diet	**Cohort**	**No Control**															
Scheiber 2001	12 wk	Soy nuts & milk				60		42	54.1	*-1.6*	NS				post♀	♀♀	C
		No control group															
Supplement	**RCT**	**Casein**															
Persky 2002	24 wk	ISP w/Isoflavones	39	26	7	72	40	22	43.7	*+0.3*		nd	*+0.9*	NS	post♀	♀♀	B
		ISP w/Isoflavones	26	14	4	43	40	24	39.7	*-2.9*			*-2.3*	NS			
		Casein						24	41.6	*-0.6*							
Teede 2001	13 wk	ISP w/Isoflavones	77	38	5	118	40	83[b]	97.4	*+1.1*	NS		*+3.7*		post♀	♀♀	C[b]
		Casein							112.7	*-2.6*	NS						
Supplement	**Xover**	**Placebo**															
Jayagopal 2002	12 wk	ISP w/Isoflavones	70	49	13	132	30	32	48.7	*-4.1*			*-2.8*	NS	post♀ DM	♀♀	B
		Cellulose							49.2	*-1.3*							
Nikander 2003 14602747	12 wk	Isoflavones	7	41	66	114	0	28	79.9	*-0.4*	NS		*+0.6*	NS	post♀ Breast CA	♀	B
		Placebo							78.8	*-1*	NS						
Supplement	**RCT**	**Placebo**															
Upmalis 2000	12 wk	Isoflavones	25	25		50	0	59	76.2	*+9.1*	NS		*+2.1*		post♀	♀♀	C
		Placebo						63	79.3	+7	NS						
Han 2002	13 wk	Isoflavones	70	19	11	100	0	40	90.3	*-23.3*	<0.01		*-4.4*	NS	post♀	I	A
		Placebo						40	84.3	*-18.9*	NS						
Petri 2004	26 wk	Soy germ capsules				60	0.8	25	76.8	*+0.9*			*-6.4*	NS	post♀	♀	B
		Lactose						25	75.2	*+7.3*							
Uesugi 2003	13 wk	Isoflavones	0	0	0	62[c]	0	11	56.5	*-0.7*	NS		*+11.9*	NS	post♀	♀	B
		Dextrin						10	73.5	*-12.6*	NS						
Knight 2001	12 wk	Isoflavones				77	0	9	74.7	*-7.3*			*+3.1*	NS	post♀	♀	C
		Placebo						11	74.3	*-10.4*							
Supplement	**Xover**	**No Control**															
Duncan 1999 10522983	13.5 wk	ISP w/Isoflavones	77	44	12	132	63	18	56.2	*-2*	NS	nd	--		post♀	♀	C
		ISP w/Isoflavones	38	22	6	65	63			*-3.6*	0.01		--				
		No control group						--									
Supplement	**Cohort**	**No Control**															
Foth 2003	24 wk	ISP w/Isoflavones	20				20	16	70.94	*+1.53*	NS		--		post♀	♀	C
		No control group						--									

[a] Soy flour = 45g/d; no other soy ingredient is quantified

[b] In contrast with other outcomes in this article, no data on how many women completed the study in each arm.

[c] 31 mg daidzin, 7mg genistin, 21 mg glycitin

3.4.3. Estradiol (E2)

(Tables 55-56)

The National Guideline Clearinghouse has included guidelines that recommend E2 should be measured in females as part of the evaluation for basic infertility, especially in women older than 35 years (www.guideline.gov/summary/summary.aspx?doc_id=5567&nbr=3764). E2 in pre-menopausal women is evaluated during the follicular phase of the menstrual cycle. Although E2 level in post-menopausal women generally is not considered of clinical importance, this report also includes the results of studies on post-menopausal women.

Study Descriptions

Six RCTs including 2 with a cross-over design, 1 non-randomized controlled trial, and 5 cohort studies reported E2 levels in healthy pre-menopausal women as an outcome (Table 55).[48,153-157,165-169] All studies reported E2 levels during the follicular phase of the menstrual cycle except for Maskarinec 2004,[165] which measured E2 levels 5 days after ovulation and Petrakis 1996,[169] which reported variability during menstrual cycles that E2 samples were collected. The largest RCT assigned 109 women in the intervention arm. None of the other RCTs had more than 33 participants in the soy arm. The non-randomized controlled trial recruited 19 pre-menopausal women in the soy arm. The other 4 cohort studies reported a sample size of 5 to 14 participants. The duration of the RCTs ranged between 12 and 48 weeks. The non-randomized trial had duration of 4 weeks as well as the cohort studies that stated a trial duration of 1 menstrual cycle each. The studies were generally of poor quality (1 B score, 11 C) with limited applicability because of the small number of participants. Four studies incorporated the soy products into the diet; the remaining supplemented diets with soy products. Seven studies investigated isolated soy protein with isoflavone, one study used only isolated soy protein, another trial used isoflavone-free soy milk, and 3 studies investigated pure soy isoflavones.

Ten RCTs including 2 with cross-over design and 4 cohort studies reported E2 levels in healthy post-menopausal women as an outcome (Table 56).[91,93,123,125,128,159-162,169-173] The RCTs recruited 11 to 53 participants in the soy arm while the cohort studies reported a sample size of 10 to 37 participants. The duration of the RCTs ranged between 12 and 52 weeks. The cohort studies lasted 4 to 24 weeks. The studies were of generally poor to moderate quality (1 A score, 6 B, 7 C) with generally limited to moderate applicability to post-menopausal women. Six studies incorporated the soy products into the diet; the remaining supplemented diets with soy products. Five studies investigated isolated soy protein with isoflavone while 1 study reported isolated soy diet; there was 1 study that used soy nuts and milk, another study provided soy flour, and another soy germ capsules. The remaining 5 studies investigated pure soy isoflavones, 2 of which only genistein.

Overall Effect

Among studies with pre-menopausal women (Table 55), Stroescu 2001, in an RCT that recruited 14 female gymnasts with primary amenorrhea from the Olympic team in Romania, reported a significant decrease in E2 levels within each group.[168] Among the cohort studies, only Cassidy 1994[153] reported a significant increase in E2 level. No other significant effect on E2 levels was found in the trials. There was one more trial, which reported that daily consumption of soy milk reduced circulating levels of estradiol by 25% ($P<0.01$) compared with levels during the home diet period but it doesn't report specific results.[163]

Among trials with post-menopausal women (Table 56), 2 RCTs reported a significant effect on E2 level in the soy arm; however, Han 2002[91] reported an increase and Duncan 1999[161] reported a decrease. Han 2002[91] also reported a significantly higher increase in E2 level in the soy arm compared with the controls. No other study showed any significant effects on E2 levels.

There were an additional 7 studies that reported E2 as an outcome without reporting specific results.[81,163,164,174-177] Only 1 cohort study on 6 healthy pre-menopausal women reported a statistically significant decrease in E2 levels after consuming soymilk for 1 month.[175]

Soy Product, Dose, Other Variables

For pre-menopausal women, given the small number of studies, it is difficult to make cross-study comparisons in regards to different types or doses of soy products investigated.

Two studies directly compared different isoflavone doses in pre-menopausal women (Table 55). Watanabe 2000[48] investigated 2 pure isoflavone products, one providing 40 mg per day and another 20 mg per day isoflavones. Both resulted in small non-significant decreases of E2 level. However, the trial did not provide information as to whether the difference between the 2 soy products was significant. Duncan 1999[156] compared 2 isolated soy protein products, one providing 128 mg per day and one 64 mg per day isoflavones. No significant change was reported between the 2 arms.

For post-menopausal women (Table 56), the only statistically significant increase in E2 was reported by Han 2002[91] in a study of pure isoflavones. However, no other study with a similar or higher amount of pure soy isoflavones found any significant effect. A small study, Duncan 1999,[48,161] reported the only significant decrease in E2 level after providing isolated soy protein with isoflavones in post-menopausal women. This result was not confirmed by any of the other studies that also investigated isolated soy protein with isoflavones.

Persky 2002[160] (Table 56) and Duncan 1999[161] (Table 55) directly compared different isoflavone doses in post-menopausal women. For Persky 2002[160] 2 isolated soy protein products, one providing 72 mg per day and one 43 mg per day isoflavones, were compared to milk protein. Both doses resulted in a small non-significant increase in E2 levels. For Duncan 1999,[161] two isolated soy protein products, one providing 132 mg per day and one 65 mg per day isoflavones, were compared to each other. As noted above, both resulted in significant decreases in E2 levels. However, neither of the 2 trials provided information whether the differences between the 2 soy products were significant.

Arjmandi 2003[170] (Table 56) performed separate sub-analyses of post-menopausal women who were receiving hormone therapy and those who were not on hormone therapy. A non-significant increase was found among women in both groups.

Summary

Six RCTs, 1 non-randomized controlled trial, and 5 cohort studies of generally poor quality and limited applicability investigated the effect of isolated soy protein or pure soy isoflavones on E2 levels among pre-menopausal women. Overall, evidence is conflicting on the effect on E2 levels of soy product consumption by pre-menopausal women. Additionally, there is insufficient evidence regarding different types or doses of soy products to compare their relative effectiveness.

Ten RCTs and 4 cohort studies of generally poor to moderate quality and limited to moderate applicability investigated the effect of isolated soy protein or pure soy isoflavones on E2 levels among post-menopausal women. Overall, evidence is conflicting on the effect on E2

level of soy consumption by post-menopausal women. Additionally, there is insufficient evidence regarding different types or doses of soy products to compare their relative effectiveness.

Table 55. Effect of soy products on estradiol (pg/mL) in pre-menopausal women

Diet/Supplement	Design	Control	Dose (mg/day)				Dose (g/day)		N	Base value	Change		Net Change		Population	Applicability	Quality
Author Year	Duration	Intervention	Genistein	Daidzein	Glycitein	T. Isoflav	Soy Protein				Value	P within	P btw Soy	Value	P vs Control			
Diet	RCT	Animal/Usual																
Maskarinec 2004	~104 wk	ISP w/Isoflavones [a]				50			100/91	150	*+2*	NS		*+16*	NS	pre♀	♂	C
		Usual diet							105/96	136	*-14*	NS						
Diet	Cohort	No control																
Cassidy 1994 [b]	~4 wk	ISP w/Isoflavones	20	25		40	60		6	66.96	*+31.64*	<0.02		--		pre♀	♂	C
		No control group							--									
Cassidy 1995 (Study 4) [b]	~4 wk	ISP w/o Isoflavones							6	81.7	*-11*	NS		--		pre♀	♂	C
		No control group							--									
Cassidy 1995 (Study 3) [b]	~4 wk	ISP w/Isoflavones							5	114.4	*-30*	NS		--		pre♀	♂	C
		No control group							--									
Supplement	RCT	Animal/Usual																
Nagata 1998	~12 wk	Soy milk				109			31	87.5	*-23.9*	NS		*-20.5*	NS	pre♀	♂	C
		Usual diet							29	86.8	*+3.4*	NS						
Supplement	RCT	Placebo																
Kumar 2002	12 wk	Isoflavones				40	0		33	44.58	*+2.68*	NS		*-1.98*	NS	pre♀	♂	C
		Placebo							33	47.39	*+4.64*	NS						
Maskarinec 2002	48 wk	Isoflavones				74	0		17	147	*-28*			*-7*	NS	pre♀	♂	B
		Maltodextrin							17	136	*-21*							
Stroescu 2001	16 wk	ISP [c]							7	nd	*-18.3*	<0.01		*-7*	NS	pre♀ [d]	♂	C
		Placebo							7	nd	*-17.4*	<0.01						
Supplement	Xover	No control																
Watanabe 2000	4 wk	Isoflavones	2	17	10	40	0		19	nd	~20	NS	nd			pre♀	♂	C
		Isoflavones	1	9	5	20	0				~25	NS						
		No control group																
Duncan 1999 9920082	13.5 wk	ISP w/Isoflavones				128			14	nd	*43.24* [e]		NS	--		pre♀	♂	C
		ISP w/Isoflavones				64					*44.9* [e]			--				
		No control group							--									
Supplement	Cohort	No control																
Petrakis 1996	4 wk	ISP w/Isoflavones	38				38		14	81.2 [f]	*+8.6*	NS		--		pre♀	♂	C
		No control group							--									
Lu 2001	~4 wk	Soy milk w/o Isoflavones					37.9		9	107	*0*	NS		--		pre♀	♂	C
		No control group							--									

[a] In Maskarinec 2004, 2 servings of soy per day were provided; the size of one serving was calculated to supply ~25 mg of isoflavones; soy foods that were used for the intervention included: tofu, soymilk, roasted soy nuts, soy protein powder, and soy bars. The amount of soy protein per serving ranged from 4.7-21.9 g; no data on the daily amount of soy protein consumption are given

[b] In the paper of Cassidy 1995, 4 cohort studies are included (S1-S4): the first has also been published as Cassidy 1994 (also reported in the table); the 2nd has been excluded because of inadequate sample size (< 5 women); the 3rd and 4th are reported in the table as Cassidy 1995 (S3) and Cassidy 1995 (S4) respectively

[c] 1g soy protein /kg body weight twice a day

[d] This study recruited 14 Romanian female gymnasts of the Olympic team with primary amenorrhea

[e] Only final values are reported in the paper

[f] No data on when the E2 measurements were performed regarding the menstrual cycle phase

Table 56. Effect of soy products on estradiol (pg/mL) in post-menopausal women

Diet/Supplement	Design	Control	Dose							Change			Net Change				
			mg/day				g/day										
Author Year	Duration	Intervention	Genistein	Daidizein	Glycitein	T. Isoflav	Soy Protein	N	Base value	Value	P within	P btw Soy	Value	P vs Control	Population	Applicability	Quality
Diet	RCT	Dairy															
Arjmandi 2003	12 wk	ISP w/Isoflavones				88	40	20	51.5	+15.1	NS		*+4.9*	NS	post♀ mixed[a]	👭	C
		Milk protein						22	84.8	+10.2	NS						
		ISP w/Isoflavones				88	40	20	93.4	+23.5	NS		*-11.96*	NS	post♀ on HRT		
		Milk protein						22	122.84	+35.46	NS						
		ISP w/Isoflavones				88	40	20	35.6	+26.1	NS		*-21.2*	NS	post♀ w/o HRT		
		Milk protein						22	45.9	+47.3	NS						
Diet	RCT	Animal/Usual															
Chiechi 2003	24 wk	ISP diet	27	19	1	47		53	10.1	-3.9			*-6*	NS	post♀	👭	C
		Usual diet						58	13.6	+2.1							
Diet	RCT	Miscellaneous															
Brooks 2004	16 wk	Soy flour	26	16	1	42		15	10.60	+9.67			*+14.64*	NS	post♀	🧍	B
		Wheat flour						15	20.11	-4.97							
Diet	Cohort	No control															
Scheiber 2001	12 wk	Soy nuts /Soy milk				60		42	17.4	*+1.5*	NS		--		post♀	👭	C
		No control						--									
Supplement	RCT	Casein															
Persky 2002	24 wk	ISP w/Isoflavones	26	14	4	43	40	24	4.8	*+1.9*	NS	nd	+2.7	NS	post♀	👭	B
		ISP w/Isoflavones	39	26	7	72	40	22	2.6	*+0.3*	NS		+1.1	NS			
		Casein						24	4.3	*-0.8*	NS						
Supplement	Xover	Placebo															
Nikander 2003 14602747	12 wk	Isoflavones	7	41	66	114	0	28	38.1	*-0.5*	NS		*-4.3*	NS	post♀ Breast CA	🧍	B
		Placebo							34.6	*+3.8*	NS						
Supplement	RCT	Placebo															
Han 2002	13 wk	Isoflavones	70	19	11	100	0	40	9	*+10*	<0.01		*+8.7*	**<0.01**	post♀	👭👭	A
		Placebo						40	9.6	*+1.3*	NS						
Morabito 2002	48 wk	Genistein	54			54	0	30	19.9	*+1.1*			*+2.2*	NS	post♀	👭	B
		Placebo						30	21	*-1.1*							
Squadrito 2003	52 wk	Genistein	54				0	27	19.6	*+0.6*			*+0.4*	NS	post♀	🧍	B
		Placebo						26	19.1	*+0.2*							
Petri 2004	26 wk	Soy germ capsules				60	0.8	25	15.8	*+1.9*			*+4.2*	NS	post♀	👭	B
		Lactose capsules						25	14.6	*-2.3*							
Supplement	Xover	No Control															
Duncan 1999 10522983	13.5 wk	ISP w/Isoflavones	77	44	12	132	63	18	9.7	*-0.2*	<0.05	nd	--		post♀	🧍	C
		ISP w/Isoflavones	38	22	6	65	63			*-1.6*	<0.05		--				
		No control group						--									
Supplement	Cohort	No Control															
Hsu 2001	24 wk	Isoflavones				150	0	37	9.6	*+11.8*	NS		--		post♀	👭	C
		No control group						--									
Foth 2003	24 wk	ISP w/Isoflavones	20				20	16	32.3	*-4.9*	NS		--		post♀	🧍	C
		No control group						--									
Petrakis 1996	4 wk	ISP w/Isoflavones	38				38	10	53.3	*-0.5*	NS		--		post♀	🧍	C
		No control group						--									

Breast CA = history of breast cancer; HRT = hormone replacement therapy

[a] The authors report in the abstract that 22 women were on hormone therapy and 20 were not on hormone therapy. They provide incorrect numbers of subjects in their sub-analyses results tables

3.4.4. Menstrual Cycle Length

(Table 57)

Study Descriptions

A total of 11 trials in 10 publications examined the effects of soy and/or its isoflavones on menstrual cycle length in pre-menopausal women.[153-156,163,166,167,174-177] The wide range of soy interventions and comparisons used in these trials makes synthesis of the data difficult; few studies were identified for each comparison category. Most of these trials are of quality C. Regardless of the large heterogeneity across the studies, 10 of the 11 trials did not show significant changes in menstrual cycle length after treatments of soy and/or its isoflavones. Only 1 RCT (Kumar 2002) showed that pre-menopausal women who took supplements of soy protein with isoflavones for 12 weeks had a significant net increase in their menstrual cycle lengths, compared with those who took the placebo (isocaloric milk protein).[167] One study by Duncan 1999 compared isolated soy protein with different doses of isoflavones and found no dose effect.[156]

Summary

No effect was observed in the studies of soy on menstrual cycle length.

Table 57. Effects of soy products on menstrual cycle length (days)

Diet /Supplement	Design	Control	Dose					N	Base value	Change			Net Change		Population	Applicability	Quality
			mg/day				g/day										
Author Year	Duration	Intervention	Genistein	Daidizein	Glycitein	T. Isoflav	Soy Protein			Value	P within	P btw Soy	Value	P vs Control			
Diet	Xover	Dairy															
Martini, 1999	2 mo	ISP w/Isoflavones	23	13		38	20	16	nd	29.3 [a]			*+0.1*	NS	pre♀ No OC	🚺🚺	C
		Skim milk							nd	29.2 [a]							
		ISP w/Isoflavones	23	13		38	20	20	nd	28.1 [a]			*+0.2*	NS	pre♀ OC		
		Skim milk							nd.	27.9 [a]							
Diet	RCT	Animal/Usual															
Nagata, 1998	2 mo	Soy milk	2.86	2.86		97		31	nd	30.7 [a]			*0*		pre♀	🚺🚺🚺	C
		Usual diet						29	nd	30.7 [a]							
Diet	NRCT	Animal/Usual															
Cassidy, 1994; Cassidy, 1995 (Study 1)	1 mo	Soy diet	20 [c]	25 [c]		45 [c]	60	6	28.5	+0.5			*+1.5*	NS	pre♀	🚺	C
		Control diet								-1.0							
Cassidy, 1995 (Study 4)	1 mo	Soy diet				23 [c]	28	6	32.0	+2.0			*+1.0*	NS	pre♀	🚺	C
		Control diet								+1.0							
Diet	NRCT	No Control															
Lu, 2000	1 mo	Soy milk	85.2	68.8		154	37.9	10	26.6	-0.6			--		pre♀	🚺	C
		No control															
Lu, 1996	1 mo	Soy milk	~100 [b]	~100[b]			nd	6	28.3	+3.5	NS		--		pre♀	🚺	C
		No control															
Wu, 2000	3 mo	Soy diet				32 [c]	nd	20	29.2	+0.1	NS		--		pre♀	🚺	C
		No control															
Supplement	RCT	Dairy															
Kumar, 2002	12 wk	ISP w/Isoflavones	40				nd	33	26.3	+3.52			*+3.6*	0.04	pre♀	🚺🚺	C
		Milk protein						33	27.8	-0.06							
Supplement	RCT	Animal/Usual															
Brown, 2002	11 mo	ISP w/Isoflavones	26	11	3	40	31	14	nd	31 [a]			*+1.8*	NS	pre♀	🚺	C
		Usual diet							nd	29.2 [a]							
Supplement	RCT	Placebo															
Maskarinec, 2002	12 mo	Isoflavones				76	0	14	29.1	--1.4			*-1.5*	NS	pre♀	🚺	B
		Placebo						14	27.4	+0.1							
Supplement	Xover	No Control															
Duncan, 1999 9920082	3 mo	ISP w/Isoflavones	70	47	10	128	53	14	29.7	*-0.4*	nd	NS	--		pre♀	🚺🚺	B
		ISP w/Isoflavones	35	24	5	64	53			*-0.5*		NS	--				
		ISP w/o Isoflavones	5	4	1	10	53			*-0.8*		NS	--				
		No control															

OC = oral contraceptives

[a] Final values
[b] 15-19% of total isoflavones were aglycones
[c] Glucosides form of isoflavones

3.4.5. Thyroid stimulating hormone (TSH)

(Table 58)

TSH is clinically important as an indicator for thyroid function. TSH is increased in secondary hypothyroidism and is considered a valuable marker for its diagnosis. Previous reports have discussed soy-induced hypothyroidism as an adverse event of soy consumption. This report focused on studies that included TSH as an outcome to explore available evidence and investigate whether hypotheses on soy induced hypothyroidism could be confirmed.

Study Descriptions

Six RCTs including 4 with cross-over design reported TSH levels in healthy subjects as an outcome.[84,156,160,161,178,179] Four trials included only post-menopausal women, 1 trial recruited pre-menopausal women, and 1 study recruited males. No study had more than 32 participants in the soy arm. The duration of the studies ranged between 4 and 24 weeks. The studies were of poor to moderate quality (2 B, 4 C) with generally limited applicability to post-menopausal women. Two studies incorporated the soy products into the diet; the remaining supplemented diets with soy products. Five studies investigated isolated soy protein with isoflavones, one of which administered the soy protein with cotyledon in one arm and with cellulose in the other arm, and also had an additional arm of soy flour. The last study provided pure soy isoflavones.

Overall Effect

Only Persky 2002[160] reported a statistically significant increase for TSH level in post-menopausal women. Although there was a trend for TSH increase in most trials with post-menopausal women, this result was not consistent for all soy arms. Ham 1993,[178] the only study that evaluated TSH level in men, reported a non-significant decrease for all the soy arms.

There were 2 additional studies both reported in single publication that described non-significant effects of soy in healthy post-menopausal women and male individuals but they did not provide specific results.[88]

Soy Product, Dose, Other Variables

Only Persky 2002[160] in a 24-week duration study reported a statistically significant increase for TSH level in the soy arm with the higher isoflavone intake compared to the casein control group. However, no significant increase was observed in other trials with even higher isoflavone intake but over a shorter duration. Only in Bruce 2003,[179] a 24-week duration study, did subjects consume approximately the same amount of isoflavones as in Persky 2002[160] but without soy protein. This trial found no significant effect, as well.

Ham 1993[178] directly compared different soy products. Soy flour and isolated soy protein with isoflavones were compared to milk protein and cellulose. All arms resulted in small non-significant decrease in TSH levels. Persky 2002[160] and 2 studies by Duncan in 1999 (in post-menopausal women[161] and in pre-menopausal women[156]) directly compared different isoflavone doses. For Persky 2002[160] 2 isolated soy protein products, one providing 72 mg per day and one 43 mg per day isoflavones, were compared to milk protein. The soy product with higher isoflavones resulted in a statistically significant increase while the soy product with lower isoflavones did not. For Duncan 1999 on post-menopausal women,[161] 2 isolated soy protein products, one providing 132 mg per day and one 65 mg per day isoflavones, were compared to

each other. The soy product with higher isoflavones resulted in an increase of TSH levels while the soy product with lower isoflavones decreased TSH. Both changes were not significant. For Duncan 1999 on pre-menopausal women,[156] 2 isolated soy protein products, one providing 128 mg per day and one 64 mg per day isoflavones, were compared to each other. No significant change was reported between the 2 arms.

Summary

Six randomized trials of generally poor to moderate quality and limited applicability investigated the effect of isolated soy protein or pure soy isoflavones on thyroid function. Overall, limited evidence suggests a possible small increase in TSH level with consumption of soy products by post-menopausal women. However, the only trial with men reported a decrease in TSH level with soy consumption. These differences were small and it is unlikely whether they could have a clinical effect on thyroid function. There is insufficient evidence regarding different types or doses of soy products to compare their relative effectiveness.

Table 58. Effect of soy products on TSH (mIU/L)

Diet /Supplement	Design	Control	Dose							Change			Net Change				
			mg/day				g/day										
Author Year	Duration	Intervention	Genistein	Daidizein	Glycitein	T. Isoflav	Soy Protein	N	Base value	Value	P within	P btw Soy	Value	P vs Control	Population	Applicability	Quality
Diet	Xover	Dairy															
Ham 1993	4 wk	Soy flour					50	17	1.8	*-0.6*	NS	nd	*+0.3*		♂	🚹	C
		ISP w/Isoflavones + cotyledon					50		1.8	*-0.6*	NS		*+0.3*				
		ISP w/Isoflavones + cellulose					50		1.8	*-0.7*	NS		*+0.4*				
		Nonfat dry milk+cellulose							1.8	*-0.3*	NS						
Supplement	RCT	Casein															
Persky 2002	24 wk	ISP w/Isoflavones	39	26	7	72	40	22	2.04	*0.18*		nd	*+0.43*	0.01			
		ISP w/Isoflavones	26	14	4	43	40	24	2.22	*-0.17*			*+0.08*	NS	post♀	🚹	B
		Casein						24	2.25	*-0.25*							
Supplement	Xover	No Control															
Duncan 1999 10522983	13.5 wk	ISP w/Isoflavones	77	44	12	132	63	18	3.48	*+0.01*	NS	NS	*+0.24*				
		ISP w/Isoflavones	38	22	6	65	63			*-0.15*	NS		*+0.08*		post♀	🚹	C
		No control								*-0.23*	NS						
Duncan 1999 9920082	13.5 wk	ISP w/Isoflavones				128		14	nd	*1.41*[a]		NS	--				
		ISP w/Isoflavones				64				*1.52*[a]			--		pre♀	🚹	C
		No control group						--									
Supplement	Xover	Placebo															
Jayagopal 2002	12 wk	ISP w/Isoflavones	70	49	13	132	30	32	2.15	*+0.12*			*+0.04*	NS	post♀	🚹	B
		Cellulose							2.18	*+0.08*							
Supplement	RCT	Placebo															
Bruce 2003	24 wk	Isoflavones				90[b]	0	21	3	*+0.49*	NS		*+0.21*		post♀	🚺🚹	C
		Maltodextrin						21	3.35	*+0.28*	NS						

[a] Only final values are reported in the paper
[b] The glycosides genistin, daidzin, and glycitin are in the ratio of 1.3:1.0:0.3. No data on amount of aglycones.

3.5. Cancer and Tumor-Related Biomarkers

(Table 59)

Twenty-five trials evaluated soy in participants without a diagnosis of cancer for risk factors or tumor markers related to the following types of cancer: breast (13 studies),[154,156,157,163,165,167,169,173,175,180-183] prostate (5),[85,150,151,184,185] endometrial (1),[103] and colon (1).[186] Five studies did not specify the type of cancer.[46,66,158,187,188] Two additional trials that enrolled women with benign or malignant breast disease also evaluated soy for risk factors or tumor markers related to breast cancer.[189], [190] These 2 trials used small portions of normal breast tissue at least 1 cm from the site of the benign or malignant breast lesion. While we include these 2 studies, it is important to note that we did not systematically look for studies of patients with cancer (where soy products may have been used as cancer treatment). Furthermore, this report does not attempt to systematically review *in vitro* or animal studies. None of the included 27 trials reported the development of cancer as an outcome.

Most of the studies investigated the effect of soy isoflavones on (serum or urinary) estrogens and estrogen metabolites as well as on estrogenicity indicators (e.g. vaginal cell maturation, increased estrogen receptor expression, increased endogenous prolactin concentration and mammary gland proliferation). Additionally, they have included biomarkers outcomes that may be related to anti-estrogenic or estrogenic activity such as progesterone receptor expression, ovarian hormone levels, (serum or urinary) gonadotrophin levels, progesterone levels, sex hormone-binding globulin (SHBG) levels, menstrual cycle length, endometrial biopsy histological dating, endometrial thickness, dehydroepiandrosterone (DHEA), free androgen index and prostate specific antigen (PSA) levels; they also have measured as outcomes insulin, insulin-like growth factor (IGF), insulin-like growth factor binding protein-3 (IGFBP-3), cortisol and thyroid hormone levels.

However, according to the National Cancer Institute (NCI), none of these markers is considered a risk factor relevant to these types of cancer (www.nci.nih.gov/cancertopics). The primary purpose of all these trials was not to examine a possible effect of soy on cancer risk factors. Instead, they mainly aimed at correlating soy protein and/or its isoflavones with the estrogen pathway, which may explain several cancer risk factors such as earlier age at menses, later age at menopause, obesity, hormone therapy, etc. There were only 3 studies that reported testosterone levels (which is a potential risk factor for prostate cancer according to NCI) as an outcome. These studies are analyzed in the endocrine results section of this report (Table 51).

There were also cancer trials that aimed to correlate soy with other possible pathways of cancer prevention. Some trials investigated the antioxidant properties of soy through outcomes such as nuclear transcription factor NF-κB in human lymphocytes and 5-hydroxymethyl-2'-deoxyuridine (5-OHmdU) in DNA from nucleated blood cells, or 8-hydroxy-2'-deoxyguanosine (8-OHdG) in urine. Phosphatidylcholine hydroperoxide (PCOOH) and phosphatidyl-ethanolamine hydroperoxide (PEOOH) in red blood cells were also outcomes in these studies. Another trial examined the potential of protein kinase inhibition by soy having as an outcome the platelet-derived growth factor (PDGF) levels. Most of these cellular tumor markers are in the experimental stage of research and are not considered cancer risk factors. Since no causal relationship could be actually established between these outcomes and cancer, their results were not considered for further analysis.

Whether soy plays a beneficial role in preventing certain types of cancer cannot be clearly hypothesized.[191] For example, despite the strong biological rationale to support a

protective effect for soy in relation to breast cancer, data from human observational studies are inconclusive. In addition to the inconsistencies in human observational studies, some laboratory evidence suggests that the isoflavones genistein and daidzein increase cell proliferation and promote the growth of estrogen-dependent mammary tumors.[192-195]

Three trials have also raised concerns that isoflavones may exert estrogenic effects on breast tissue. Petrakis 1996 reported an increase in the presence of epithelial hyperplasia in nipple aspirate fluid from pre-menopausal and post-menopausal healthy women following a 6-month soy protein intervention.[169] Hargreaves 1999 and McMichael-Phillips 1998 reported changes in estrogen-regulated proteins in nipple aspirate fluid that were indicative of an estrogenic response among pre-menopausal women with benign or malignant breast disease following a 14-day soy protein intervention.[189] , [190] Stimulation of cell proliferation in breast tissue increases breast density, which is suggested as a potential biomarker of estrogenic or anti-estrogenic effects of a treatment on breast tissue. Breast density is assessed by mammography as a percentage of the breast occupied by dense tissue, or as the absolute area of dense tissue. It is not yet clear, however, whether one method of expressing breast density is preferable over the other. Using mammographic breast density as an intermediate risk marker for breast cancer risk, the reports by Maskarinec 2003 and 2004 showed no significant differences in mammographic breast density that could be attributed to soy intervention.[165,182] However, neither breast cell proliferation as indicated by epithelial hyperplasia nor mammographic breast density are established risk factors for breast cancer and no further inferences can be drawn from these studies.

Table 59 Summary of tumor-related biomarker trials

Author year	Soy product	Study Design	Population	Target tissue	# subjects analyzed in soy arm(s)	Outcomes	Mechanism
Adams 2003	Isolated soy protein w/isoflavone	RCT	healthy adults with adenomatous colorectal polyps	colorectal	150	insulin-like growth factors (IGF), low IGF binding protein-3 (IGFBP-3)	estrogenic activity
Baird 1995	Textured soy protein + isoflavone	RCT	healthy post-menopausal women	ND	66	vaginal cytology, LH, FSH, SHBG, estradiol	estrogenic activity
Bazzoli 2002	Isolated soy protein w/isoflavone	RCT	healthy pre-menopausal women	breast	9	Lipid peroxides, urinary 8-hydroxy-2'-deoxyguanosine, total antioxidant status	antioxidant properties
Cassidy 1995	Textured soy protein (+/-) isoflavone	2 Non controlled clinical trials 1 randomized cross-over	healthy pre-menopausal women	breast	6 6 5	menstrual cycle length, urinary LH, serum gonadotrophins, progesterone, oestradiol, SHBG	anti-estrogenic activity
Davis 2001	Soy isoflavone mixture	Non controlled clinical trial	healthy men	prostate	6	NF-kB in human lymphocytes, 5-OHmdU levels (endogenous status of cellular oxidative stress)	antioxidant properties
Djuric 2001	Soy isoflavone	Non controlled clinical trial	healthy adults	ND	12	5-OHmdU levels	antioxidant properties
Duncan 1999 9920082	Isolated soy protein w/isoflavone	Randomized cross-over	healthy pre-menopausal women	breast	14	urinary estrogens and estrogen metabolites, serum estrogens, androgens, thyroid hormones, Prolactin, gonadotrophins, SHBG, Insulin, cortisol, menstrual cycle length, endometrial biopsy histological dating	anti-estrogenic activity
Gardner-Thorpe 2003	other soy food (soy flour)	Randomized cross-over (double blind)	healthy non-smoking men	prostate	20	dihydrotestosterone (DHT), testosterone, oestradiol, estrone, sex hormone-binding globulin (SHBG), hydroperoxides, lag time copper, lag time myeloperoxidase	estrogenic activity, antioxidant properties
Habito 2000	tofu	RCT	Healthy Caucausian adult males	prostate	42	dihydrotestosterone (DHT), testosterone, oestradiol, androstanediol glucuronide, sex hormone-binding globulin (SHBG), free androgen index, testosterone/estradiol	estrogenic activity

continued

Table 59. Continued.

Author year	Soy product	Study Design	Population	Target tissue	# subjects analyzed in soy arm(s)	Outcomes	Mechanism
Hargreaves 1999	Isolated soy protein w/isoflavone	Non controlled clinical trial	Pre-menopausal women with benign or malignant breast disease	breast	84	nipple aspirate apolipoprotein D levels, ps2 protein levels, epithelial cell proliferation, estrogen and progesterone receptor status, apoptosis, mitosis, Bcl-2 expression	estrogenic activity
Hsu 2001	Soy isoflavone	Non controlled clinical trial	normal post-menopausal women	breast	37	plasma estradiol	estrogenic activity
Jenkins 2003	Soy-based diet	Randomized cross-over	middle-aged men	prostate	46	serum PSA	estrogenic activity
Kumar 2002	Isolated soy protein w/isoflavone	RCT (double blind)	healthy pre-menopausal women	breast	66	serum estrone, estradiol and SHBG, menstrual cycle length	anti-estrogenic activity
Lu 2001	Soy-milk without isoflavones	Non controlled clinical trial	healthy pre-menopausal women	breast	9	serum ovarian hormones, gonadotropins	anti-estrogenic activity
Lu 2000	Soy-milk	Non controlled clinical trial	healthy pre-menopausal women	breast	10	serum ovarian hormones, gonadotropins	anti-estrogenic activity
Lu 1996	Soy-milk	Non controlled clinical trial	healthy pre-menopausal women	breast	6	serum 17b-estradiol, progesterone and DHEA, menstrual cycle length	anti-estrogenic activity
Luz 2000	Soy-milk	Non controlled clinical trial	healthy pre-menopausal women	breast	8	urinary estrogen metabolites	anti-estrogenic activity
Maskarinec 2004	Tofu Soy-milk Other soy food (roasted soy nuts, soy protein powder, soy bars)	RCT	Pre-menopausal women	breast	109	mammogram density assessment estradiol, estrone, progesterone, SHBG, androstenedione	anti-estrogenic activity
Maskarinec 2003	Soy isoflavone	RCT	Pre-menopausal women	breast	15	mammogram density assessment	anti-estrogenic activity
McMichael –Phillips 1998	Isolated soy protein w/isoflavone	RCT	Pre-menopausal women with benign or malignant breast disease	breast	48	epithelial cell proliferation, progesterone receptor status	estrogenic activity
Murkies 1995	other soy food (soy flour)	RCT (double blind)	Post-menopausal women	ND	28	vaginal maturation index	estrogenic activity
Murray 2003	Isolated soy protein w/isoflavone	RCT (double blind)	healthy post-menopausal women	endometrial	16 (2 arms)	endometrial thickness	anti-estrogenic activity

continued

Table 59. Continued.

Author year	Soy product	Study Design	Population	Target tissue	# subjects analyzed in soy arm(s)	Outcomes	Mechanism
Nagata 2001	Soy milk	RCT	Healthy men	prostate	17	total testosterone, free testosterone, estrone, estradiol,SHBG	estrogenic activity
Petrakis 1996	Isolated soy protein w/ isoflavone	Non controlled clinical trial	Healthy caucasian pre- and postmenopausal women (2 cohorts)	breast	37	Nipple aspirate fluid (NAF) volume; gross cystic disease fluid protein (GCDFP-15) concentration; NAF cytology; estradiol, progesterone, prolactin, SHBG	anti-estrogenic activity
Ross 1995	tofu	Non controlled clinical trial	healthy adults	ND	23	platelet-derived growth factor (PDGF)	inhibition of protein tyrosine kinases
Scambia 2000	Soy extract w/isoflavone	RCT (double blind)	Post-menopausal women	ND	20	endometrial thickness, vaginal maturation index	estrogenic activity
Xu 2000	Isolated soy protein w/ isoflavone	Randomized cross-over	healthy post-menopausal women	breast	18	urinary estrogens and estrogen metabolites	anti-estrogenic activity

3.6. Osteoporosis and Osteoporosis Risk Factors

(Tables 60-64)

Bone mineral density (BMD) is a composite of bone mineral content (BMC) and cross sectional area of bone. Both BMD and BMC measurements are thought to be the best approach for screening individuals with risk of osteoporosis and the major determinant of fracture risk. Other factors affecting fracture risk are the bone turnover rate and the microarchitecture of the bone. BMD and BMC measurements, however, do not measure the actual bone turnover and a long follow-up time is required to detect any change. Bone turnover can be estimated from various biomarkers of bone formation (serum osteocalcin, total and bone specific alkaline phosphatase, procollagen type I carboxy terminal propeptide, and procollagen type I amino terminal propeptide) and that of bone resorption (urinary hydroxyproline, galactosyl hydroxylysine, total and free pyridinoline, total and free deoxypyridinoline, collagen type I cross linked N-telopeptide, and collagen type I cross linked C-telopeptide, tartrate resistant acid phosphatase, and serum type I collagen carboxy terminal telopeptide).[196]

A total of 26 studies are included in this section. Ten trials examined the effects of soy and/or its isoflavones on bone mineral density (BMD) and/or bone mineral contents (BMC). Though 5 of these did not meet criteria because of their short duration for BMD (less than 1 year) they are also discussed briefly.The effects of soy and/or its isoflavones on bone biomarkers related to bone turnover or bone remodeling were reported in 22 studies. (Tables 60-64).

Table 60. Summary of studies evaluating bone endpoints

Author, Year	BMD	BMC[a]	Bone biomarkers						
			Resorption				Formation		All other markers reported in the study
			HP	Pyr	D-pyr	NTx	OC	bAP	
Alekel, 2000	X[b]	X[b]				X[d]		X[d]	Urinary calcium
Anderson, 2002	X	X							
Arjmandi, 2003					X			X	Urinary calcium, phosphorus and magnesium
Brooks, 2004					X			X	
Chen, 2004	X	X							
Chiechi, 2002 12191852	X[b]	X[b]	X	X		X	X		
Dalais, 2003				X	X				
Gallagher, 2004	X[b]					X	X		
Jones, 2003				X				X	
Katsuyama, 2004						X	X	X	Urinary calcium, bone stiffness
Khalil, 2002					X[e]			X[e]	
Kreijkamp-Kaspers, 2004	X							X	Plasma calcium and phosphorus
Lydeking Olsen, 2004	X	X							Serum type I procollagen-N-terminal-peptide, collagen type I cross linked C-telopeptide
Mackey, 2000					X		X[c]	X[c]	
Morabito, 2002	X			X	X		X	X	Urinary and blood calcium
Murkies, 1995			X						Urinary calcium
Murray, 2003						X			
Nikander, 2004				X	X	X		X	Procollagen type I carboxy terminal propeptide, procollagen type I amino terminal propeptide
Potter, 1998	X[b]	X[b]							
Scheiber, 2001						X	X	X	
Uesugi, 2002				X	X		X		Bone stiffness
Uesugi, 2003	X[b]			X					Urinary calcium
Upmalis, 2000						X	X		
Wangen, 2000					X		X	X	Collagen type I cross linked C-telopeptide
Yamaguchi, 2001							X		Urinary calcium
Yamori, 2002				X	X				Bone stiffness
Total numbers of studies	10	6	2	8	10	8	10	12	

BMD = bone mineral density; BMC = bone mineral contents; HP = urinary hydroxyproline; Pyr = urinary pyridinoline; D-pyr = urinary deoxypyridinoline; NTx = urinary collagen type I cross linked N-telopeptide; OC = serum osteocalcin; bAP = serum bone specific alkaline phosphatase

[a] BMC was not evaluated in this report.
[b] Studies that did not meet criteria for BMD analyses due to short duration (< 1 year intervention).
[c] Results were not summarized in the summary tables due to lack of baseline and final data reported. The authors stated that there were no significant changes in both OC and bAP markers after the intervention.
[d] Results were not summarized in the summary tables due to lack of final data reported. The authors stated that there were no significant changes in both bAP and NTx markers after the intervention.
[e] Results were not summarized in the summary tables due to lack of final data reported. The authors stated that there were no significant changes in both deoxypyridinoline and NTx markers after the intervention.

Table 61. Number of bone studies included with different study designs (and total)

Study Design	BMD (1 year minimum duration)	Bone Formation Biomarkers	Bone Resorption Biomarkers
Parallel	5	13	16
Cross-over	0	2	2
Single-Cohort trial	0	2	2
Total	**5**	**17**	**20**

Table 62. Number of bone studies included within each population and quality category

	BMD (1 year minimum duration)				Bone Formation Biomarkers				Bone Resorption Biomarkers			
Quality		A	B	C		A	B	C		A	B	C
Population Category	**Total**	**0**	**3**	**2**	**Total**	**1**	**6**	**10**	**Total**	**1**	**6**	**13**
Post-Menop Women	**4**	1	2	1	**12**	2	2	8	**15**	1	4	10
Peri-Menop Women	**0**	0	0	0	**1**	0	0	1	**1**	0	0	1
Pre-Menop Women	**1**	0	0	1	**2**	0	1	1	**3**	0	1	2
Men or Teenage Boys	**0**	0	0	0	**3**	0	2	1	**2**	0	1	1

BMD = bone mineral density; BMC = bone mineral contents; Post-Menop = post-menopausal; Pre-Menop = pre-menopausal

Table 63. Number of bone studies (or study arms) included that used different types of soy products, controls, or soy consumption types (diet versus supplement)

	BMD (1 year minimum duration)	Bone Formation Biomarkers	Bone Resorption Biomarkers
Soy Product (Study Arms)			
Protein with Isoflavones	3	13	14
Protein without Isoflavones	2	2	3
Isoflavones	2	4	6
Control Types (Study Arms)			
Dairy	1	3	4
Animal/Usual Diet	0	2	1
Placebo	2	5	7
Miscellaneous	0	2	4
No Non-Soy Control	2	4	3
Diet or Supplement (Studies)			
Diet	0	5	7
Supplement	5	13	14

BMD = bone mineral density; BMC = bone mineral contents

Table 64. Number of bone studies that directly compared the effects of different soy product characteristics or study subject characteristics

Comparison Characteristics	BMD (1 year minimum duration)	Bone Formation Biomarkers	Bone Resorption Biomarkers
Protein with *v* without Isoflavones	2	4	3
Different Soy Protein Dosages	0	1	1
Different Soy Isoflavone Dosages	1	3	2
Different Population Categories	0	1	1

BMD = bone mineral density; BMC = bone mineral contents

3.6.1. Bone Mineral Density (BMD)

(Tables 65-67)

BMD and BMC in healthy adults are maintained if there is a balance of bone formation and bone resorption (normal bone turnover or remodeling rate). Post-menopausal women may have rapid decline of BMD due to estrogen deficiency. Research has showed the yearly BMD decline in post-menopausal women is at least 1% and up to 2.4%.[197]

Study Descriptions

Since all 5 qualified studies reported BMD (in 6 publications),[78,172,198-201] but only 3 also reported BMC data, we focus on BMD outcomes. BMD was measured in lumbar spine (Table 65), femoral neck (Table 66), and hip (Table 67) locations. Only 1 study is in pre-menopausal women while the other 4 studies are in post-menopausal women. There is 1 high-quality study, while the quality of the remaining studies are of medium or poor quality. Five studies that otherwise would have qualified were excluded for BMD analyses due to the short duration (<1 year intervention).[87,97,108,202,203]

Among the 3 milk-protein or placebo controlled trials, only Morabito 2002[172] found that a purified soy isoflavone extract (54 mg per day of genistein) consistently increased lumbar spine (Table 65), and femoral neck (Table 66) BMD after 1-year intervention in post-menopausal women. Hip BMD was not measured in this study. The other 2 trials found small or inconsistent effects.

Two studies compared soy with isoflavones to soy without isoflavones. Neither included a non-soy control. Lydeking-Olsen 2004[200] found that soy milk with isoflavones yielded a small increase in lumbar spine BMD, which was significantly different than the larger decrease in BMD with soy milk lacking isoflavones (Table 65). This effect was not seen in femoral neck BMD (Table 66) or by Anderson 2002.[201]

Results from short-term studies (not included in Summary Tables) were similar to the long-term studies. The treatment durations were of 3 months in 1 study,[97], of 6 months in 3 studies [108,202,203], and of 9 months in 1 study.[87] Four of these short-term studies showed no significant treatment effect of soy and/or its isoflavones on lumbar spine and/or femoral neck BMD compared to the control. Only Potter 1998 found that lumbar spine BMD increased significantly in the high-dose group (soy protein with 90 mg/day of total isoflavones) compared to control.[108] No significant change was seen in the low-dose group (soy protein with 56 mg/day of total isoflavones.

Summary

Because there are few long-term RCTs and a wide variety of soy interventions used across studies, it is difficult to draw an overall conclusion about the effects of soy on bone outcomes. Overall, among the 5 studies of 1 year minimum duration, no consistent effect on BMD was seen with soy consumption. Studies of shorter duration, likewise found no effect of soy.

Table 65. Effects of soy products on lumbar spine bone mineral density (g/cm^2)

Diet /Supplement	Design	Control	Dose							% Change			Net % Change		Population	Applicability	Quality
			mg/day				g/day										
Author Year	Duration	Intervention	Genistein	Daidizein	Glycitein	T. Isoflav	Soy Protein	N	Base value	Value	P within	P btw Soy	Value	P vs Control			
Supplement	RCT	Dairy															
Kreijkamp-Kaspers 2004 [a]	1 yr	ISP w/Isoflavones	52	41	6		26	88	0.92	*+0.02*			-0.01	NS	post♀		A
		Milk protein						87	0.90	*-0.02*							
Supplement	RCT	Placebo															
Chen 2004; 2003[b]	1 yr	Isoflavones	6	19	16	40	0	57		-0.5	NS	NS	*+0.2*		post♀		C
		Isoflavones	12	38	31	80	0	50		-0.9	NS		*-0.3*				
		Placebo						53		-0.6	NS						
Morabito 2002	1 yr	Isoflavones	54				0	30	0.92	+3			*+4.6*	<0.04	post♀		B
		Placebo	0					30	0.93	-1.6							
Supplement	RCT	No Control															
Lydeking-Olsen 2004	2 yr	Soymilk w/Isoflavones				76	18	23	0.93	+1.1	NS	0.01	--		post♀		B
		Soymilk w/o Isoflavones				1	18	22	0.87	-4.2	.006		--				
		No control						--									
Anderson 2002	1 yr	ISP w/Isoflavones	>50 [c]			90 [c]		15	1.04	+1	NS	NS	--		pre♀ (21-25 yr)		C
		ISP w/o Isoflavones				0		13	1.01	0	NS		--				
		No control						--									

[a] Apparent discrepancies between Within-Cohort changes and Between-Cohort changes are due to rounding errors in estimated Within-Cohort changes compared to reported Between-Cohort changes.

[b] Data reported for completers only. The noncompliant subjects or those lost to follow up had significantly higher BMD at all measured sites

[c] Calculated from 59%:41% isoflavones as glucosides:aglycones

Table 66. Effects of soy products on femoral neck bone mineral density (g/cm^2)

Diet /Supplement	Design	Control	Dose							% Change			Net % Change		Population	Applicability	Quality
			mg/day				g/day										
Author Year	Duration	Intervention	Genistein	Daidizein	Glycitein	T. Isoflav	Soy Protein	N	Base value	Value	P within	P btw Soy	Value	P vs Control			
Supplement	RCT	Placebo															
Chen 2004; 2003[a]	1 yr	Isoflavones	12	38	31	80	0	50		+0.1	NS		*+0.1*		post♀		C
		Isoflavones	6	19	16	40	0	57		-0.5	NS		*-0.5*				
		Corn starch						53		+0.04	NS						
Morabito 2002	1 yr	Isoflavones	54				0	30	0.69	+3.6			*+4.3*	<0.001	post♀		B
		Placebo						30	0.69	-0.7							
Supplement	RCT	No Control															
Lydeking-Olsen 2004	2 yr	Soymilk w/Isoflavones				76	18	23		-0.9	NS	NS	--		post♀		B
		Soymilk w/o Isoflavones				1	18	22		+0.2	NS		--				
		No control															
Anderson 2002	1 yr	ISP w/Isoflavones	>21 [b]			36 [c]		15	0.93	-3	0.01	NS	--		pre♀ (21-25 yr)		C
		ISP w/o Isoflavones				0		13	0.89	-1	NS		--				
		No control															

[a] Data reported for completers only. The noncompliant subjects or those lost to follow up had significantly higher BMD at all measured sites

[b] Calculated from 59%:41% isoflavones as glucosides:aglycones

Table 67. Effects of soy products on hip bone mineral density (g/cm^2)

Diet /Supplement	Design	Control	Dose						N	Base value	% Change			Net % Change		Population	Applicability	Quality
			mg/day				g/day											
Author Year	Duration	Intervention	Genistein	Daidizein	Glycitein	T. Isoflav	Soy Protein				Value	P within	P btw Soy	Value	P vs Control			
Supplement	RCT	Dairy																
Kreijkamp-Kaspers 2004 [a]	1 yr	ISP w/Isoflavones	52	41	6		26		88	0.86	*-0.1*			+0.4	NS	post♀	🚹🚺	A
		Milk protein							87	0.83	*-0.5*							
Supplement	RCT	Placebo																
Chen 2004; 2003 [b]	1 yr	Isoflavones	6	19	16	40	0		57		-0.5	NS		*+0.03*		post♀	🚹🚺🚺	C
		Isoflavones	12	38	31	80	0		50		-0.2	NS		*+0.3*				
		Corn starch							53		-0.5	NS						

[a] Apparent discrepancies between Within-Cohort changes and Between-Cohort changes are due to rounding errors in estimated Within-Cohort changes compared to reported Between-Cohort changes.

[b] Data reported for completers only. The noncompliant subjects or those lost to follow up had significantly higher BMD at all measured sites.

3.6.2. Bone Formation Biomarkers

(Tables 68-69)

Bone specific alkaline phosphatase (bAP) measurements can be used as a bone formation marker because it is thought to participate in the initiation of bone mineralization. Post-menopausal women have higher levels of bone specific alkaline phosphatase than pre-menopausal women have. Serum osteocalcin (OC), also known as bone GLA protein, is another bone formation marker. It is a bone specific non-collagenous protein and is thought to be a sensitive and specific marker of osteoblastic activity whose serum levels reflect the rate of bone formation.[196]

Study Descriptions

Nine studies examined the effects of soy and/or its isoflavones on bAP (Table 68);[78,128,138,170-172,204-206] 9 evaluated OC (Table 69).[47,87,96,128,172,203,204,206,207] Three additional studies reported only no significant changes in either bAP or OC with soy intervention.[88,202,208] Some studies reported on both biomarkers so that their results appear in both summary tables. Among these studies, there are 8 RCTs, 2 cross-over trials, and 2 non-controlled trials. The majority of these trials enrolled pre- and post-menopausal women. One study included both men and women, 1 study included peri-menopausal women and 2 studies included men or teenage boys only. There are 2 high-quality studies and the remaining studies are of quality B or C.

No statistically significant effect was reported for bone formation as measured by OC and bAP by most of the studies. Only the study by Morabito 2002,[172] which was the also the only study to find a significant benefit of soy on BMD and which used soy genistein 54 mg per day compared to placebo, found that genistein significantly increased bone formation as indicated by the increase in both OC and bAP biomarkers. Wangen 2000 and Gallagher 2004, 2 low-quality trials compared isolated soy protein with different doses of isoflavones and showed trends toward reduced concentrations of OC and/or bAP by the high-isoflavone group.[87,206]

Summary

Overall, across studies, the evidence does not suggest any consistent or statistically significant effect of soy products on bAP or OC, 2 biomarkers of bone formation.

Table 68. Effects of soy products on bone formation biomarkers: serum bone specific alkaline phosphatase (bAP)

Diet /Supplement	Design	Control	Dose									% Change			Net % Change					
			mg/day				g/day													
Author Year	Duration	Intervention	Genistein	Daidzein	Glycitein	T. Isoflav	Soy Protein	N	Base value	Unit	Value	P within	P btw Soy	Value	P vs Control	Population	Applicability	Quality
Diet	RCT	Animal/Usual																
Katsuyama 2004	1 yr	90 g Natto per wk					16[d]	18	64	U/L	*+10*		<0.05	*+11*	NS	pre♀	🧍	C
		30 g Natto per wk					5[d]	16	52		*-14*			*-13*	NS			
		30 g Natto per mo					5[d]	21	54		*+3.5*		NS	*+4.5*	NS			
		Usual diet						18	61		*-1.0*							
Diet	RCT	Miscellaneous																
Brooks, 2004	16 wk	Soy muffins	26	16	1	42	15	13	15.9	U/L	*-0.73*	NS		+1.49	NS	post♀	🧍	B
		Placebo muffins						15	15.6		+0.76	NS						
Diet	Cohort	No Control																
Scheiber 2001	12 wk	Soy nuts and drinks					~60	42	19	µg/L	*+5.8*	NS		--		post♀	🧍🧍🧍	C
		No control																
Supplement	RCT	Dairy																
Kreijkamp-Kaspers 2004 [e]	1 yr	ISP w/Isoflavones	52	41	6		26	88	13	µg/L	*-4.6*			*-0.8*	NS	post♀	🧍🧍	A
		Milk protein						87	13		*-3.8*							
Arjmandi 2003	3 mo	ISP w/Isoflavones				88	40	20[c]	26	U/L	*-0.1*	NS		*+0.1*		post♀	🧍	C
		Milk protein						22[c]	23		*-0.2*	0.05						
Supplement	Xover	Placebo																
Nikander 2004 15001611	3 mo	Isoflavones	7	41	66	114	0	56	14.6	µg/L	0	NS		*-0.5*	NS	post♀ BrCA	🧍	A
		Placebo							14.7		+0.5	0.02						
Supplement	RCT	Placebo																
Jones 2003	6 wk	Isoflavones				50	0	69	46	U/L	+10	<0.05		+0.5	NS	♂ Teen	🧍	B
		Placebo						59	49		+8	<0.05						
Morabito 2002	1 yr	Isoflavones	54				0	30	9.7	µg/L	+24			*+20*	<0.05	post♀	🧍	B
		Placebo						30	10		-4							
Supplement	Xover	No control																
Wangen, 2000	93 days	ISP w/Isoflavones				132	63	17	21	U/L	+6.7	<.05	NS	--		post♀	🧍	C
		ISP w/Isoflavones				65	63				+6.7	<.05		--				
		ISP w/o Isoflavones				7	63				+17.6	<.05	<0.05	--				
		No control																

BrCA = breast cancer

[a] Median value, estimated from graph
[b] U/L, converted from 1:0.01667 µkat/L:U/L
[c] The authors report in the abstract that 22 women were on hormone therapy and 20 were not on hormone therapy.
[d] Soy protein was estimated from USDA database (www.nal.usda.gov/fnic/foodcomp/cgi-bin/measure.pl) for 30 gram Natto.
[e] Apparent discrepancies between Within-Cohort changes and Between-Cohort changes are due to rounding errors in estimated Within-Cohort changes compared to reported Between-Cohort changes.

Table 69. Effects of soy products on bone formation biomarkers: serum osteocalcin (OC, ng/mL)

Diet /Supplement	Design	Control	Dose					N	Base value	Change		Net Change				
			mg/day				g/day									
Author Year	Duration	Intervention	Genistein	Daidzein	Glycitein	T. Isoflav	Soy Protein			Value	P within	P btw Soy	Value	P vs Control	Population	Applicability	Quality
Diet	RCT	Animal/Usual															
Chiechi 2002 12191852	6 mo	ISP w/Isoflavones				47		53/24	21.9	+5.45	<0.05		*+3.8*	NS	post♀		C
		Control						58/43	15.5	+1.7	NS						
Katsuyama 2004	1 yr	90 g Natto per wk					16[d]	18	1.68	+1.18			*+1.2*	NS	pre♀		C
		30 g Natto per wk					5.3[d]	16	1.95	+0.22		NS	*+0.2*	NS			
		30 g Natto per mo					5.3[d]	21	1.42	-0.29			*+0.3*	NS			
		Usual diet						18	1.91	-0.01							
Diet	Cohort	No Control															
Scheiber 2001	12 wk	Soy nuts and drinks				~60		42	5.8	+0.6	<0.03		--		post♀		C
		No control						--									
Supplement	RCT	Placebo															
Morabito 2002	1 yr	Isoflavones	54				0	30	13	*+5*			*+6*	<0.05	post♀		B
		Placebo						30	13	*-1*							
Upmalis 2000	12 wk	Isoflavones	50[c]				0	59	13	*+0.3*	NS		*-0.8*		post♀		C
		Placebo						63	14	*+1.1*	NS						
Uesugi 2002	4 wk	ISP w/Isoflavones				62	16.4	12	8.5	*-1.1*	NS		*-1.0*	NS	pre♀		B
		Placebo						11	7.2	*-0.1*	NS						
Supplement	Xover	No control															
Wangen, 2000	93 days	ISP w/Isoflavones				132	63	17	2.5[b]	+0.36	NS	NS	--		post♀		C
		ISP w/Isoflavones				65	63			+0.6	NS		--				
		ISP w/o Isoflavones				7	63			+0.6	NS		--				
		No control															
Supplement	RCT	No Control															
Gallagher 2004	9 mo	ISP w/Isoflavones	52	28		96	40	17	32.8	0[f]	NS		--		post♀		C
		ISP w/Isoflavones	28	20		52	40	19	25.9	0[f]	NS		--				
		ISP w/Isoflavones	4			<4	40	14	24.3	+1.7[f]	NS		--				
		No control															
Supplement	Cohort	No Control															
Yamaguchi 2001	60 d	Nijiru powder[e]	0.02[e]	0.02[e]				12	9.9[f]	+10[f]	<0.01		--		♂♀		C
								6	10[f]	+9[f]	<0.01		--		♂		
								6	9.8[f]	+11[f]	<0.01		--		♀		
		No control						-									

E_2 = exogenous estradiol

[a] Median value, estimated from graph
[b] Unit = nmol/L
[c] 50 mg genistein and daidzein
[d] Soy protein was estimated from USDA database (www.nal.usda.gov/fnic/foodcomp/cgi-bin/measure.pl) for 30 gram Natto
[e] Nijiru powder is a byproduct of natto. It also contains 2.7 mg of daidzin and 2.4 mg of genistin per day
[f] Value was estimated from graph

3.6.3. Bone Resorption Biomarkers

Urinary hydroxyproline, which is an amino acid in the collagen structure, has been used for a long time as a biomarker for measuring bone resorption. When collagen degradation is accelerated during bone resorption, urinary hydroxyproline increases. However, urinary hydroxyproline is not a sensitive biomarker because the majority of the hydroxyproline derived from the breakdown of collagen is reabsorbed by the renal tubules and degraded in the liver. There are now several biomarkers of bone resorption that are more sensitive. As shown in Figure 11, peptide chain of collagen has amino (N) and carboxy (C) terminals from which N-telopeptides and C-telopeptides are covalently bound to collagen by pyridinoline (Pyr) and deoxypyridinoline (D-pyr) cross-links. When collagen is degraded, pyridinoline and D-pyridinoline are released into the circulation, where 20% is free and the remaining is protein bound. The protein bound fraction binds either to N-telopeptide, as collagen type I cross-linked N-telopeptide (NTx) or to C-telopeptide (CTx). The total, free, or protein bound pyridinoline and D-pyridinoline can be measured as bone resorption markers.[196]

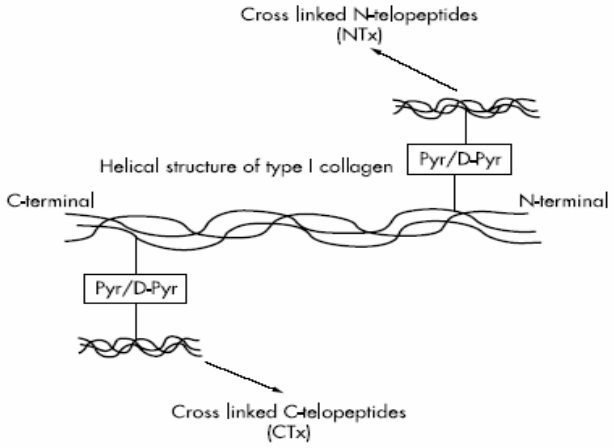


Figure 11. Cross linked N- and C-telopeptides of type I collagen. Source: Dogan and Posaci. Postgrad.Med.J. 2002; 78(926):727-31

3.6.3.a. Urinary Hydroxyproline

(Table 70)

Study Descriptions

Two RCTs reported urinary hydroxyproline as a bone resorption biomarker in post-menopausal women.[66,203] They are both of poor quality. No significant effects were found comparing soy protein with isoflavones from diet to control diets. Notably, Murkies 1995 found that bone resorption significantly increased in the control group but not in the soy flour group.[66]

Summary

Inconsistent and non-significant effects were observed in the 2 RCTs evaluating urinary hydroxyproline.

Table 70. Effects of soy products on urinary hydroxyproline (mmol/24 hours)

Diet /Supplement Author Year	Design Duration	Control Intervention	Dose mg/day Genistein	Daidizein	Glycitein	T. Isoflav	g/day Soy Protein	N	Base value	Change Value	Change P within	Change P btw Soy	Net Change Value	Net Change P vs Control	Population	Applicability	Quality
Diet	RCT	Animal/Usual															
Chiechi 2002 12191852	6 mo	ISP w/Isoflavones					47	53/24	55.3 [a]	-6.12	NS		*-1.5*	NS	post♀		C
		Control						58/43	50.7 [a]	-4.6	NS						
Diet	RCT	Miscellaneous															
Murkies 1995	12 wks	Soy flour	40 g of flour per day					23	186.2	*+14.6*	NS		*-40.1*	NS	post♀		C
		Wheat flour						24	181.6	*+54.7*	<0.05						

[a] Unit used was not reported clearly ("hydroxyproline/creatine")

3.6.3.b. Urinary Cross-Linked N-telopeptide (NTx)

(Table 71)

Study Descriptions

A total of 8 trials reported NTx as a bone resorption biomarker.[47,87,103,128,138,202-204] Most of these trials are of poor quality. Katsuyama 2004,in pre-menopausal women[204] and Alekel 2000, in peri-menopausal women[202] found no significant effects of diets of soy protein with or without isoflavones compared to the control diets, regardless of dose in either study.

The other 6 studies were in post-menopausal women, including 1 trial in post-menopausal women with breast cancer. These 6 studies are very heterogeneous: 1 soy diet RCT, 1 soy diet uncontrolled cohort, 2 soy isoflavones trials (1 cross-over and 1 RCT), 1 RCT of soy protein with isoflavones in combination of hormone replacement therapy, and 1 RCT compared the effects of soy protein with different amount of isoflavones. Regardless of the heterogeneity across the 6 trials of post-menopausal women, there was no significant effect of soy and/or its isoflavones when compared to the placebo treatments. Scheiber 2001, a prospective uncontrolled cohort of soy nuts and soy drinks, showed that the post-menopausal women received the soy dietary intervention had significantly reduced urinary NTx levels.[128]

Gallagher 2004,[87] an RCT without a non-soy control, found no dose-response relationship of soy protein with different dose of isoflavones. While among the women who consumed soy with the highest dose of isoflavones did have a statistically significant decrease in NTx, in contrast to the women consuming lower doses of isoflavones, the magnitude of the change was the same as for those not consuming soy isoflavones and they had a substantially higher baseline NTx level.

Summary

There is no consistent effect of soy protein and/or its isoflavones on urinary NTx levels compared to the control treatments in pre-, peri- and post-menopausal women. However, the poor quality of these trials might contribute to the inconsistent findings.

Table 71. Effects of soy products on urinary cross-linked N-telopeptide (NTx, nmol BCE/mmol creatinine)

Diet /Supplement	Design	Control	Dose									Change			Net Change				
			mg/day				g/day												
Author Year	Duration	Intervention	Genistein	Daidizein	Glycitein	T. Isoflav	Soy Protein	N	Base value	Value	P within	P btw Soy	Value	P vs Control	Population	Applicability	Quality
Diet	RCT	Animal/Usual															
Katsuyama 2004	1 yr	90 g Natto per week					16[b]	18	46.7	-2.2		NS	*+0.5*[c]	NS	pre♀	🧍	C
		30 g Natto per week					5[b]	16	36.0	-11.7[c]			*-9.0*[c]	NS			
		30 g Natto per month					5[b]	21	45.8	-12.0			*-9.3*[c]	NS			
		Usual diet						18	35.7	-2.7[c]							
Diet	RCT	Miscellaneous															
Chiechi 2002 12191852	6 mo	ISP w/Isoflavones				47		53/24	29.5[g]	+4.9	NS		*+3.6*		post♀	🧍	C
		Control						58/43	29.9[g]	+1.3	NS						
Alekel 2000	6 mo	ISP w/Isoflavones				80	40	24	65[a]		NS	NS		NS	peri♀	🧍🧍🧍	C
		ISP w/o Isoflavones				4	40	24	67[a]		NS			NS			
		Whey protein						21	55[a]		NS						
Diet	Cohort	No Control															
Scheiber 2001	12 wk	Soy nuts and soy drinks				~60		42	52	-7.3	<0.02		--		post♀	🧍🧍🧍	C
		No control															
Supplement	Xover	Placebo															
Nikander 2004 15001611	3 mo	Isoflavones	7	41	66	114	0	56	71.9	-2.4	NS		*-5.5*	NS	post♀ BrCA	🧍	A
		Placebo							73.7	+3.1	NS						
Supplement	RCT	Placebo															
Upmalis 2000	12 wk	Isoflavones	50[d]				0	59	52.6[g]	*+0.7*			*+2.1*		post♀	🧍	C
		Placebo						63	54.8[g]	*-1.4*							
Murray 2003	6 mo	ISP w/Isoflavones + 0.5 mg E_2	66	44	10	120	38	8	18.5[e]	*-5.1*	NS		*-1.6*	NS	post♀	🧍	C
		Placebo + 0.5 mg E_2						7	16.8[e]	*-3.5*	0.02						
		ISP w/Isoflavones + 1.0 mg E_2	66	44	10	120	38	8	15.1[e]	*-3.9*	0.02		*+2.5*	NS			
		Placebo + 1.0 mg E_2						7	17.0[e]	*-6.4*	0.03						
Supplement	RCT	No Control															
Gallagher 2004	9 mo	ISP w/Isoflavones	52	28		96	40	17	94.2	-4[f]	NS	<0.05	--		post♀	🧍🧍	C
		ISP w/Isoflavones	28	20		52	40	19	60.8	-0.8[f]	NS	NS	--				
		ISP w/o Isoflavones	4			<4	40	14	60.9	-4[f]	NS	NS	--				
		No control															

E_2 = exogenous estradiol; BrCA = breast cancer

[a] Median value, estimated from graph
[b] Soy protein was estimated from USDA database (www.nal.usda.gov/fnic/foodcomp/cgi-bin/measure.pl) for 30 g Natto
[c] According to reported baseline and final mean values, for 90 g per week net change = -1.4; for 30 g per week change = -8.3 and net change = -7.5; for 30 g per month net change = -11.2; for usual diet change = -0.8.
[d] 50 mg genistein and daidizein
[e] Unit = nM bone collagen equivalents
[f] Value was estimated from graph
[g] Unit used was not clear

3.6.3.c. Urinary Pyridinoline

(Table 72)

Study Descriptions

Eight trials reported urinary pyridinoline as a bone resorption biomarker.[96,138,170,172,203,205,209,210] One study was of good quality, 4 of moderate quality, and 3 of poor quality. Five RCTs were conducted in post-menopausal women, 1 cross-over trial was in post-menopausal women with breast cancer, 1 RCT was in teenage boys, and 1 RCT was in pre-menopausal women.

Of the 5 RCTs in post-menopausal women, all showed a net reduction in the urinary pyridinoline after the soy protein and/or its isoflavones treatments compared to the control treatments. However, only Morabito 2002 reported a significant effect.[172] This study, which used soy genistein 54 mg per day in comparison with placebo, was also the only study to find a significant effect on BMD and biomarkers of bone formation. It found that genistein significantly reduced bone resorption as indicated by the decrease in urinary pyridinoline. The RCT of soy protein with isoflavones in pre-menopausal women (Uesugi 2002) also found a significant net reduction in urinary pyridinoline compared to the placebo.[96] Non-significant net reductions in urinary pyridinoline were found in the cross-over trial of soy isoflavones among post-menopausal women with breast cancer and in the RCT of soy isoflavones among teenage boys.

Summary

There is some evidence to suggest that soy protein and/or its isoflavones might reduce urinary pyridinoline levels in both pre-menopausal and post-menopausal women. However, the evidence is limited given that few studies found a statistically significant effect and the large degree of heterogeneity across studies.

Table 72. Effects of soy products on urinary pyridinoline (nmol/umol creatinine)

Diet /Supplement	Design	Control	Dose							Change			Net Change				
			mg/day				g/day										
Author Year	Duration	Intervention	Genistein	Daidizein	Glycitein	T. Isoflav	Soy Protein	N	Base value	Value	P within	P btw Soy	Value	P vs Control	Population	Applicability	Quality
Diet	RCT	Animal/Usual															
Chiechi 2002 12191852	6 mo	ISP w/Isoflavones				47		53/24	nd	-6.12	NS		*-1.5*		post♀	🚹	C
		Usual diet						58/43	nd	-4.60	NS						
Diet	RCT	Miscellaneous															
Yamori, 2002	10 wk	Soybean and sesame	6	21	11	37	6	20	3.04	*-0.95*	<0.05		*-0.47*	NS	post♀	🚹	B
		Sesame						20	2.65	*-0.48*	NS						
Supplement	RCT	Dairy															
Arjmandi 2003	3 mo	ISP w/Isoflavones				88	40	20[c]	9.62	*-2.43*	0.01		*-1.56*	NS	post♀	🚹	C
		Milk protein						22[c]	7.66	*-0.87*	NS						
Supplement	Xover	Placebo															
Nikander 2004 15001611	3 mo	Isoflavones	7	41	66	114	0	56	7.95	-0.82	0.001		-0.82		post♀ BrCA	🚹	A
		Placebo							7.48	-0.03	NS						
Supplement	RCT	Placebo															
Jones 2003	6 wk	Isoflavones				50	0	69	8.72	+0.36			*-0.44*	NS	♂ Teen	🚹	B
		Placebo						59	9.29	+0.77							
Morabito 2002	1 yr	Isoflavones	54				0	30	11.2	-4.7	<0.05		*-4.0*	<0.05	post♀	🚹	B
		Placebo	0					30	9.9	-0.7	NS						
Uesugi 2002	4 wk	ISP w/Isoflavones				62	16	12	19.7	-6.6	<0.05		*-8.0*	<0.05	pre♀	🚹	B
		Placebo						11	16.2	+1.4	NS						
Supplement	RCT	Miscellaneous															
Dalais, 2003	3 mo	ISP w/Isoflavones				118	40	37	7.07	-0.38			*-0.30*	NS	post♀	🚺🚹	C
		Wheat protein						40	7.35	-0.08							

3.6.3.d. Urinary Deoxypyridinoline

(Table 73)

Study Descriptions

Ten trials reported on urinary deoxypyridinoline.[88,96,97,138,171,172,206,208-210] The majority of these trials are of moderate quality. Eight trials were conducted in post-menopausal women, 2 of which were of dietary soy, the others of soy supplements. One of these studies included women with breast cancer, 1 in pre-menopausal women, and 1 in men.

Among the 8 trials of post-menopausal women, all but Dalais 2003[210] found a net reduction in urinary deoxypyridinoline with soy consumption; however, the reduction was statistically significant in only half the studies and the net effects ranged from +0.4 to –6.5 nmol/mmol creatinine. In the 2 studies by Wangen 2000[206] and Mackey 2000[88] that compared different doses of soy isoflavones (although did not include a non-soy control), no dose-effect was seen. No dose-effect was evident across studies either, where isoflavone doses ranged from 4 to 132 mg per day and reported soy protein doses ranged from 6 to 63 g per day (in addition to studies without soy protein).

The single study of pre-menopausal women (Uesugi 2002[96]) found asignificnat reduction in urinary deoxypyridinoline among women consuming soy protein with isoflavones, but this effect was not significantly different than the reduction in women in the control arm.

Khalil 2002[208] evaluated the effect of soy protein with isoflavones on urinary deoxypyridinoline among men. Detailed results were not reported; however, no significant difference in effect was reported for all men and for subgroups based on age.

Summary

Among women, almost all studies reported reductions and net reductions in urinary deoxypyridinoline with soy consumption. However the range of effects was broad and only half the studies (of post-menopausal women) reported significant effects. No dose-effect for either soy isoflavones or soy protein was evident.

Table 73. Effects of soy products on urinary deoxypyridinoline (nmol/mmol creatinine)

Diet /Supplement	Design	Control	Dose					N	Base value	Change			Net Change		Population	Applicability	Quality
			mg/day				g/day										
Author Year	Duration	Intervention	Genistein	Daidzein	Glycitein	T. Isoflav	Soy Protein			Value	P within	P btw Soy	Value	P vs Control			
Diet	RCT	Miscellaneous															
Yamori, 2002	10 wk	Soybean and sesame	6	21	11	37	6	20	7.6	-2.8	NS		*-3.5*	<0.05	post♀	♂	B
		Sesame						20	5.2	+0.7	NS						
Brooks, 2004	16 wk	Soy muffins	26	16	1	42	15	13	9.52	-0.54	NS		*-0.85*	NS	post♀	♂	B
		Placebo muffins						15	9.01	+0.31	NS						
Supplement	RCT	Dairy															
Supplement	Xover	Placebo															
Nikander 2004 15001611	3 mo	Isoflavones	7	41	66	114	0	56	19.7	-2.0	0.008		*-2.4*	<0.05	post♀ BrCA	♂	A
		Placebo							18.9	+0.4	NS						
Supplement	RCT	Placebo															
Morabito 2002	1 yr	Isoflavones	54				0	30	27[a]	*-12*	<0.05		*-11*	<0.05	post♀	♂	B
		Placebo	0					30	23[a]	*-1*	NS						
Uesugi 2002	4 wk	ISP w/Isoflavones				62	16	12	11.7	*-1.9*	<0.05		*-1.1*	NS	pre♀	♂	B
		Placebo						11	10.1	*-0.8*	NS						
Uesugi 2003	3 mo	Isoflavones	7[b]	31[b]	21[b]	62[b]	0	11	13.7	*-6.9*	<0.01		*-6.5*	0.01	post♀	♂	B
		Placebo						10	12.9	*-0.4*	NS						
Supplement	RCT	Miscellaneous															
Dalais, 2003	3 mo	ISP w/Isoflavones				118	40	37	15.29	-0.8			+0.4	NS	post♀	♂♂	C
		Wheat protein						40	14.47	-0.3							
Supplement	Xover	No Control															
Wangen, 2000	93 days	ISP w/Isoflavones				132	63	17	6.84	*-0.52*	NS	NS	--		post♀	♂	C
		ISP w/Isoflavones				65	63			*-0.07*	NS		--				
		ISP w/o Isoflavones				7	63			-0.73	NS		--				
		No control															
Supplement	RCT	No Control															
Mackey 2000	12 wk	ISP w/Isoflavones				65		25	8.9[d]	*-0.64*	0.01	NS			post♀	♂♂	C[d]
		ISP w/o Isoflavones				4		24									
		No control															

[a] pmol/mmol creatinine
[b] glucosides
[c] The authors reported in the abstract that 22 women were on hormone replacement therapy and 20 were not
[d] Data were reported for both arms combined. The authors stated that the observed change was due largely to group ISP w/o isoflavones although no statistical change was found between groups. Limited data was in contrast to other outcomes reported in this article.

3.6.4. Summary of Osteoporosis and Osteoporosis Risk Factors Studies

Overall, 31 studies evaluated various markers of bone health, including BMD, bone formation biomarkers (bAP and OC) and bone resorption biomarkers (urinary hydroxyproline, urinary NTx, urinary pyridinoline, and urinary deoxypyridinoline).

Studies of BMD and of bone formation biomarkers generally found no effect of soy consumption when compared to control. While a number of studies reported reductions in 2 markers of bone resorption – urinary pyridinoline and deoxypyridinoline – no effects were found on the other markers of bone resorption and the effects were not consistent across studies. For these markers there is no clear evidence of a dose effect for either soy isoflavones or soy protein.

Only one study found a consistent effect on these markers. Morabito 2002 was the only study to find a significant increase in BMD or on markers of bone formation and among the few studies to find a significant reduction on markers of bone resorption.[172] They compared genistein 54 mg per day for 1 year to placebo in 30 post-menopausal women. Several factors might explain the more positive results from this study. First, this is the only study that excluded subjects with denser femoral neck BMD (>0.795 g/cm^2, which corresponds to a T score of –1 standard deviation). Thus the subjects recruited into this study had a lower BMD at femoral neck at baseline than about 50% of general population. Second, the preparation of the purified genistein tablets used in this study is also unique and may have different properties than other preparations of soy isoflavone extracts.

3.7. Reproductive Health

We included 11 trials with results on menstrual cycle length. We also included 5 trials with results on testosterone level in men, 2 trials with results on FSH in men, 6 trials with results on FSH in pre-menopausal women, and 12 trials with results on E2 in pre-menopausal women. These trials are described under *Endocrine Function*, in sections 3.4.1-4.

3.8. Miscellaneous Outcomes

This section summarizes the studies that evaluated the effects of soy and/or its isoflavones on various health conditions not included in previous sections. There is very limited evidence regarding these topics. These topics include cognitive function, kidney function, and glucose metabolism.

3.8.1. Kidney Function

(Table 74)

Only 1 study of poor quality and limited applicability assessed the effects of soy protein on kidney function.[211] We did not evaluate other kidney-related outcomes, such as nephrolithiasis and its risk factors. The study reported on 8 men with insulin treated type 2 diabetes, obesity, hypertension and proteinuria (with excretion between 50 and 1000 mg/day), who were enrolled in a cross-over study involving a soy protein and an animal protein diet each for 8 weeks. The study showed that there was no significant change in glomerular filtration rate or creatinine clearance after 8 weeks of soy protein vs. animal protein diet. There is no explanation, though, why the measurements of glomerular filtration rate and creatinine clearance are so radically different.

Table 74. Effects of soy protein diet on glomerular filtration rate and creatinine clearance

Author Year	Duration	Intervention	Dose						N	Base value	% Change			Net % Change		Population	Applicability	Quality
			mg/day				g/day											
			Genistein	Daidizein	Glycitein	T. Isoflav	Soy Protein			GFR CrCl	Value	P within	P btw Soy	Value	P vs Control			
Diet	Xover	Animal/Usual																
Anderson, 1998	8 wk	Soy protein diet					1 g/1 kg body weight		8	49 99	-5 -12	--	*0* *+8*	NS NS		♂	🧍	C
		Animal-protein diet								49 103	-5 -20							

GFR = Glomerular Filtration Rate; CrCl = Creatinine Clearance

3.8.2. Cognitive Function

(Tables 75-76)

Study Descriptions

Four studies examined the effects of soy products on cognitive function.[78,147-149] The studies include a total of 261 post-menopausal women and 27 male and female college students. None of these subjects had Alzheimer disease, dementia or mental retardation at baseline, as indicated by the average scores on the Mini-Mental State Examination (MMSE) or IQ (Intelligence quotient). All 3 studies on post-menopausal women are RCTs, of which, 2 studies of medium quality used isoflavone supplements and the other of high quality used an isolated soy protein supplement. The fourth study on male and female college students was a low quality RCT of a soy diet intervention.

Various measures of cognitive function were used across the studies (Table 75). Notably, the 2 studies reported by Duffy 2003 and File 2001 were from the same group of investigatorswho used the same protocols for testing subjects' cognitive functions.[147,148] The results of these 4 studies are summarized in Table 76.

Table 75. Cognitive function tests used

First author, year	Cognitive Function Tests
Duffy, 2003	• Verbal IQ: National Adult Reading Test revised version (NART-R) • Tests of Attention: Digit symbol substitution, Digit cancellation; Paced Auditory Serial Addition test • Tests of Memory: Short-story test a (from the Weschler Memory Scale – revised), Delayed Matching to Sample Test from the Cambridge Neuropsychological Test Automated Battery (CANTAB; CeNeS Ltd, Cambridge), Picture test; Category generation task. • Tests of Frontal Function: Verbal fluency, Test of rule shifting and reversal
File, 2001	• Verbal IQ: National Adult Reading Test revised version (NART-R) • Tests of Attention: Digit symbol substitution, Digit cancellation; Paced Auditory Serial Addition test • Tests of Memory: Short-story test a (from the Weschler Memory Scale – revised), Delayed Matching to Sample Test from the Cambridge Neuropsychological Test Automated Battery (CANTAB; CeNeS Ltd, Cambridge), Picture test; Category generation task. • Tests of Frontal Function: Verbal fluency, Test of rule shifting and reversal
Kritz-Silverstein, 2003	• Mini-Mental State Examination • Tests of Memory: Trails A andrails B (from the Halstead-Reitan Neuropsychological Test Battery), Category fluency; Logical memory and recall
Kreijkamp-Kaspers, 2004	• Tests of Memory: Rey Auditory Verbal Learning Test (immediate recall, delay recall; recognition); Digit span (forward and reversed); Doors test • Tests of Complex Attention: Trailmaking test (A1, A2; B); Digital symbol substitution • Verbal tasks: Fluency N, Fluency A, Fluency animals; Fluency occupations • Boston naming task • Mini-Mental State Examination

Kreijkamp-Kaspers 2004, a high quality study, compared soy protein with isoflavones to milk protein and found no significant differences in any of the cognitive function tests between the groups of post-menopausal women after 1-year treatments.[78] This study alone contributed about 60% of the total subjects evaluated by all 4 studies. The other 2 studies in post-menopausal women found that performance in some cognitive function tests were significantly improved in the soy isoflavones group compared to the placebo group.[147,149] However, the test instruments used by the 3 studies were all different, limiting their comparability. The only study in young male and female college students by File 2001 showed that high soy diet resulted in significant

improvements in short-term and long-term memory and in mental flexibility compared to low soy diets. The diets had no effect on tests of attention or in a category generation task.

Table 76. Effects of soy products on cognitive function

Diet /Supplement Author Year	Design Duration	Control Intervention	Dose mg/day Genistein	Daidizein	Glycitein	T. Isoflav	g/day Soy Protein	N	Cognitive Function Tests	Population	Applicability	Quality
Diet	RCT	No Control										
File, 2001	10 wk	High soy				100		~13-14[a]	High soy diet showed significant improvements in short-term (immediate recall of prose and 4 sec delayed matching to sample of patterns) and long-term memory (picture recall after 20 min) and in mental flexibility (rule shifting and reversal). In a letter fluency test and in a test of planning (Stockings of Cambridge), the high soy diet improved performance only in females. There was no effect of diet on tests of attention or in a category generation task.	♂ Pre♀	↑	C
		Low soy				0.5		~13-14[a]				
		No Control						--				
Supplement	RCT	Dairy										
Kreijkamp-Kaspers, 2004	1 yr	ISP w/Isoflavones	52	41	6		26	88	No significant differences in any of the cognitive function tests between the groups.	post♀	↑	A
		Milk protein						87				
Supplement	RCT	Placebo										
Kritz-Silverstein, 2003	6 mo	Isoflavones				110	0	27	Performance in category fluency in the soy isoflavones group improved by 23% between baseline and follow-up, whereas the performance in the placebo group improved only by 3% (P=0.02) No significant differences in any other cognitive function tests between the groups.	post♀	↑	B
		Placebo						26				
Duffy, 2003	12 wk	Isoflavones				60	0	18	Soy isoflavones group showed significantly greater improvement in delay recall of pictures, in immediate story recall tests, and in PASAT. Groups did not differ in any other cognitive function tests.	post♀	↑	B
		Lactose						15				

DMST = Delayed Matching to Sample Test; PASAT = Paced Auditory Serial Addition Test
[a] 27 students were randomly allocated to the 2 groups

Summary

The few available studies are too heterogeneous to draw an overall conclusion regarding the effects of soy protein and/or its isoflavones on cognitive function. The only long-term and high quality study showed no significant differences in any of the cognitive function tests between the groups of post-menopausal women consuming soy protein with isoflavones or milk protein.

3.8.3. Glucose Metabolism

(Tables 77-78)

Six studies reported the effects of soy intervention on fasting blood glucose in non-diabetic populations (Table 77).[23,34,89,91,104,212] One additional study reported only no significant effect on fasting blood glucose.[75] Nikander 2004 also included the results of a 2-hour oral glucose tolerance test (Table 78).[89] In the study by Onning 1998,[104] 12 healthy men and women consumed oat milk and soy milk for 4 weeks each, and 12 healthy men and women consumed oat milk and cow's milk also for 4 weeks each. The 6 women who received the soy intervention had a net increase of blood glucose of 5.4 mg/dL (P=0.05) compared to baseline diet. The 6 men who received the soy intervention had a net decrease of blood glucose of 3.6 mg/dL (P=0.01) compared to baseline diet. The combined (men and women) result, however, did not show significant change.

All 7 studies, including the one that did not report data, found no significant changes in fasting blood glucose (or glucose tolerance test) with soy intervention.

Table 77. Effects of soy products on fasting blood glucose

Author Year	Design / Duration	Control / Intervention	Dose mg/day Genistein	Daidizein	Glycitein	T. Isoflav	Dose g/day Soy Protein	N	Base value	Change Value	Change P within	Change P btw Soy	Net Change Value	Net Change P vs Control	Population	Applicability	Quality
Diet	Xover	Animal/Usual															
Huff, 1984	6 wk	Soybean diet					41	5	ND	*76*[c]			*-10*	NS	♂		C
		Mixed diet							ND	86[c]							
Diet	NRCT	Animal/Usual															
Yamashita, 1998	16 wk	ISP w/Isoflavones					130	17	82.8	*+1.8*	NS		*0*	NS	post♀		C
		Red meat diet						19	84.6	*+1.8*	NS				Obese		
Supplement	RCT	Dairy															
Onning, 1998	4 wk	Soy milk					23/30[a]	12	95.4	+1.8	NS		0		♀♂		B
		Milk						11	93.6	+1.8	NS						
		Soy milk					23	6	95.4	+5.4	0.05		+5.4		♀		
		Milk						5	93.6	0	NS						
		Soy milk					30	6	95.4	-3.6	0.01		-5.4		♂		
		Milk						6	93.6	+1.8	NS						
Supplement	Xover	Placebo															
Washburn, 1999	6 wk	ISP w/Isoflavones once daily				34	14	51/42[b]	91.7	*+0.9*	NS			NS	peri♀		B
		ISP w/Isoflavones twice daily				34	14			*+0.6*	NS			NS			
		Carbohydrates								*+0.1*	NS						
Nikander, 2004 15240647	13 wk	Isoflavones	6	42	66	114		56	91.8	*+9*	NS		*+9*	NS	post♀		A
		Placebo							91.8	*0*	NS						
Supplement	RCT	Placebo															
Han, 2002	13 wk	Isoflavones	70	19	11	100	0	40	95.6	*+1.8*	NS		*+4.7*	NS	post♀		A
		Placebo						40	96.8	*-2.9*	NS						

[a] Women/Men values
[b] Baseline/Final values
[c] Final values were used due to no baseline value was reported.

Table 78. Effects of soy products on 2-hour oral glucose tolerance test

Diet /Supplement	Design	Control	Dose							Change			Net Change					
			mg/day				g/day											
Author Year	Duration	Intervention	Genistein	Daidzein	Glycitein	T. Isoflav	Soy Protein	N	Base value	Value	P within	P btw Soy	Value	P vs Control	Population	Applicability	Quality
Supplement	Xover	Placebo																
Nikander, 2004 15240647	13 wk	Isoflavones	6	42	66	114		56	106.2	*-7.2*	NS		*-12.6*		post♀	🚻	A
		Placebo							108	*+5.4*	NS						

3.8.4. Other Miscellaneous Outcomes

(Table 79)

Included in this table, for completeness, are 7 studies that evaluated the effect of soy on a miscellaneous collection of biomarkers and outcomes that are unrelated to the health conditions examined in the previous sections.[185,188,213-217] No analyses were performed for this group of studies.

Table 79. Other miscellaneous soy studies

Author, Year	Soy Interventions	Outcome Measures
Jenkins, 2003	Soy foods	Serum Prostate Specific Antigen
Laskowski, 2003	Soy protein supplement	Adaptation process in young judoists
Lenn, 2002	Soy isolate	Delayed Onset Muscle Soreness
Pap, 1983	Soy flour diet	Secretin-pancreozymin
Pap, 1984	Soy flour & cholecystokinin-octapeptide	Pancreatic enzyme secretory capacity
Ross, 1995	Soy diet	Platelet-derived growth factor
Saxena, 1999	Soybean	Platelet factor 3 availability test

3.9. Association of Dose and Product Type with Effects

Key Question 3: *What is the scientific evidence of a dose-response effect of different forms of soy and individual constituents of soy for the conditions specified in Key Question 1?*

Each outcome section in Chapter 3 (3.2-3.8) discusses the evidence for any associations between outcomes and both dose of either soy protein or soy isoflavones and type of soy product. In order to provide clearer answer to the Key Questions on dose-response effect and different product effects, we summarize the evidence here.

Dose-Response effect

To examine the question of possible dose-response effect we both looked across studies, comparing effects in different studies that evaluated soy products with different doses, and we summarized those studies that directly compared soy products with different doses. The large majority of these studies with direct comparisons compared soy products with the same amount of soy protein but differing amounts of soy isoflavones. Few studies compared soy products with different doses of soy protein.

Overall, across studies, for all examined outcomes, we either found no association between soy dose and treatment effect or the available studies were too few or too heterogeneous to make an assessment. Few of the studies that made direct comparisons found clinically significant or statistically significant difference in treatment effect based on soy protein or isoflavone dose. Below, we summarize the data for each outcome.

Cardiovascular

Only for lipids and blood pressure are there sufficient studies to attempt to satisfactorily answer this question using data from across studies. Among the lipid studies (total cholesterol, LDL, HDL, and triglycerides), despite a wide range of treatment effects found across studies and wide ranges of doses of both soy protein and soy isoflavones used, little evidence of a dose-response was found across studies. Meta-regression of the LDL studies did find a statistically significant association between increasing soy protein dose and increasing beneficial effect of soy, but only in the subset of studies with mean baseline LDL greater than 130 mg/dL. However, when studies with minimal soy protein (<10 g/day) were omitted the association disappeared. No association was found between soy protein dose and effect on HDL, triglycerides, or blood pressure. Also, soy isoflavone dose was not associated with effect in any analysis. The 4 studies that directly compared the effect of different doses of soy protein on lipids were inconclusive regarding the association with change in lipid levels. The 14 studies that directly compared the effect of different doses of soy isoflavones on lipids almost all found no association with change in lipid levels. Likewise, across studies of lipoprotein (a) no dose-response effect was found. The 6 studies that directly compared different isoflavone doses and the 2 that compared different soy protein doses also found no association.

Similarly for blood pressure, no difference in effect was seen across studies related to either soy protein or soy isoflavone dose. Only a single study compared different doses of isoflavones and found no difference in effect. For the remaining cardiovascular outcomes examined (CRP, homocysteine, endothelial function, systemic arterial compliance, and oxidized LDL) there were either too few studies or outcome metrics were too heterogeneous to allow for

cross-study comparisons of dose. One study compared the effect of different doses of isoflavones on CRP, homocysteine, endothelial function, and oxidized LDL and found no difference for any outcome. An additional study also found no difference in effect on homocysteine with different isoflavone doses.

Menopausal Symptoms

Despite the large number of studies that evaluated menopausal symptoms, comparing effects across studies was hampered by the large variety of different outcome metrics used. Nevertheless, no difference in effect was evident based on soy protein or isoflavone dose. Three studies directly compared different doses of isoflavones (2 in peri-menopausal women). Two of the 3 studies reported either clinically or statistically significant differences based on whether the soy product contained isoflavones. In both, consumption of soy protein with isoflavones reduced menopausal symptoms compared to consumption of soy protein without isoflavones. The third study, however, found no difference across a range of isoflavone doses.

Endocrine Function

Although only 5 studies reported the effect of soy products on TSH and no difference in effect was evident across studies based on isoflavone or soy protein dose, 2 of these studies compared different doses of isoflavones. Both studies reported larger increases in TSH when subjects consumed higher isoflavone-dose products, although neither reported whether the difference was significantly different than with the lower dose products.

Too few studies evaluated FSH levels in men or pre-menopausal women to assess a dose-effect. Across the 14 studies of FSH in post-menopausal women, though, no dose effect was evident. Two studies that compared different isoflavone-dose products both found decreases in FSH in women on lower dose products and either increases or no effect with higher dose products. Although it is unclear if this difference is meaningful.

Among both pre-menopausal and post-menopausal women, no dose effect was evident for estradiol. The 3 studies that compared different doses of isoflavones likewise found no difference in effect based on dose. There were too few studies of testosterone in men to assess a possible dose effect.

Across studies menstrual cycle length was not affected by soy product consumption, regardless of dose. The one study that compared different doses of soy isoflavones found no dose effect.

Osteoporosis and Osteoporosis Risk Factors

Bone mineral density was evaluated after 1 to 2 years of treatment by only 5 studies, precluding meaningful cross-study comparisons. Two of the studies directly compared different doses of isoflavones and found no difference in effect. Likewise, across studies of osteocalcin, bone specific alkaline phosphatase, urinary cross-linked N-telopeptide, urinary pyridinoline, and urinary deoxypyridinoline no dose-effects were evident across studies. One study compared different soy protein doses (of natto) for several of the outcomes and found no consistent or significant differences in effect. The small number of studies of different isoflavone doses also found no difference in effect. With only 2 studies of urinary hydroxyproline, neither of which directly compared different doses, no conclusion about a dose effect can be made.

Cognitive Function

The small number of studies and heterogeneity in outcome measures makes cross-study comparisons of dose effect difficult. However, 1 study did report a significantly greater improvement in verbal episodic immediate memory and non-verbal episodic long-term memory with high-isoflavone-dose soy compared to soy without isoflavones.

Kidney Function

Only a single study evaluated kidney function with only a single soy product.

Glucose Metabolism

No significant effect was seen in any of the small number of studies of glucose metabolism. No study compared different doses.

Soy Product Effects

Similar to how we evaluated possible dose effects, to compare the effects of different soy products we both looked across studies, comparing effects in different studies that evaluated different soy products and we summarized those studies that directly compared soy products.

No study compared different types of soy products. All studies that compared different soy products compared similar types of products which varied either in amount of total product or dose of either soy protein or soy product. The most frequent comparison was between formulations of isolated soy protein with isoflavones and specifically designed similar isolated soy protein with either all or some of the isoflavones removed. There are no comparisons between different products such as comparing tofu to soy milk or soy milk to isolated soy protein beverages. Given the great heterogeneity among all the studies in terms of such factors as soy protein dosage, soy isoflavone dose, non-soy control, mode of consumption, study duration, and study design, it is not possible to parse out any possible differences across studies based on brand or type of product. Differences based on soy product type defined as soy protein with isoflavones versus soy protein without isoflavones are discussed above where there are relevant data in sections 3.2 to 3.8.

3.10. Adverse Events Associated with Soy Intake

(Tables 80-86)

Key Question 4: *What are the frequency and type(s) of adverse events associated with use of soy that are reported in the scientific literature (both trials and epidemiology)?*

Key Question 5: *What is the scientific evidence of a dose-response effect of whole soy products and individual soy constituents on their safety?*

We reviewed 272 clinical articles for potentially relevant human data on adverse events associated with soy foods, soy proteins, and other soy products, such as purified isoflavones. These articles included studies of clinical outcomes and risk factors and encompassed RCTs, cross-over studies, non-randomized comparison studies, cohorts and other observational studies among men and women. Most of these studies met eligibility criteria for evaluation of the health effects of soy. However, studies that failed to meet criteria due to such factors as short study duration or small sample size were also reviewed for reporting of adverse events. Of the 272 articles reviewed, 213 of them did not report either the presence or absence of adverse events. Of the remaining 59 articles, a variety of adverse events were reported in 46 studies and 3 safety/pharmacokinetic studies. There were 10 RCTs which explicitly stated that no adverse events occurred. We also reviewed 2,384 abstracts from TOXLINE to identify subsequent reports of adverse events of soy. One additional case control study was identified.

The 49 studies reporting adverse events included 3,518 subjects, about half of whom were exposed to purified isoflavones (Table 80, randomized trials),[47,89-93,125,139,155,167,172,198] soy-enriched diets or beverages (Table 81, randomized trials)[62,63,67,79,136,165,200,218-223] or isolated soy protein supplements with and without isoflavones (Table 82, randomized parallel trials,[52,55,77,78,81,103,117,133,170,224] and Table 83, cross-over trials[70,74,76,84,102,225]). Five single cohort studies (Table 84)[128,162,226-228] and 3 safety and pharmacokinetic studies (Table 85)[229-231] also reported adverse events. Ten randomized trials reported only that there were no adverse events (Table 86).[73,75,83,96,141,160,201,202,232,233] The comparators in the studies included milk, milk protein powders, whey, casein, and other placebos. The amount of soy protein in the trials ranged from 20 to 60 g/day, and isoflavones from 40 to 134 mg/day.

We did not perform meta-analysis on any of the adverse events because of the heterogeneity and inadequate reporting across the studies. Meta-analysis would lend a level of precision that is unwarranted given the poor quality and poorly detailed and overall reporting of the data. Instead we simply provide a crude percentage of the events in the text.

Two trials reported a large number of adverse events. In one study, 202 post-menopausal women in an RCT by Kreijkamp-Kaspers 2004[78] (Table 82) consumed either 25.6 g of soy protein enriched with 99 mg isoflavones or 25.6 g of milk protein for 1 year. The authors reported 511 adverse events, almost equally divided between soy and placebo groups. The adverse events were recorded every 3 months. There were a total of 48 GI complaints for soy and 33 for placebo. Each arm reported 16 urogenital complaints (urinary tract or vaginal infections). The mean number of any adverse events per participant was 2.54 in the soy group and 2.56 in the placebo group. There were no differences in types of adverse events (musculoskeletal complaints, urogenital, dermatological, respiratory, and miscellaneous) or in the rates of drop-out between the 2 groups.

The RCT by Maskarinec 2004 (Table 80) also reported a large number of adverse events, 126 in the soy group and 157 in the control.[165] There were 111 healthy pre-menopausal women who consumed either 2 daily servings of soy foods containing about 50 mg per day isoflavones or a regular diet for 2 years. The authors concluded that there was no evidence for adverse effects due to soy. They reported that collectively there were 96 upper respiratory infections, 31 musculoskeletal, 23 gynecologic or GI disorders, 11 headaches or psychological symptoms, the remaining being skin conditions, bladder infections, asthma, dental problems, high blood pressure, and diabetes. However, it is unclear how these events were distributed in the two groups. In addition, 3 women in the control group were diagnosed with breast cancer during the study and one woman in the intervention group developed breast cancer after the completion of the study.

The range of durations across studies that reported adverse events was 2 weeks to 2 years. The majority of studies evaluated a few dozen subjects for 4 to 24 weeks. Generally, the trials that reported the highest rates of adverse events were those that lasted from 1 to 2 years; however, several studies of considerably shorter duration had similar rates of adverse events. For example, among the isoflavone intervention studies (Table 80), Chen 2003[198] reported 29 adverse events after 1 year, but Secreto 2004[139] reported more than 30 after 12 weeks in a similar number of subjects. A stronger predictor of total number of adverse events than study duration appeared to be how frequently subjects were asked to record incidents.

Gastrointestinal Disturbances

Gastrointestinal (GI) disturbances were the most frequently reported adverse events. These included diverse symptoms such as heartburn, stomach pain or disorder or discomfort or swelling, abdominal distension, bloating, flatulence, constipation, or diarrhea, which occurred in 30 of the 41 comparison studies and in 4 of the 5 cohorts. Specifically, for the 12 isoflavone trials (Table 80) there were 16 GI complaints in the soy arms out of a total of 575 (2.8%) compared to 9 out of 514 controls (1.8%); in the 13 soy diet and beverages studies (Table 81) there were 30 GI complaints out of a total of 528 subjects (5.7%) versus 3 in the control arms (0.1%); for the 16 soy protein randomized parallel trials (Table 82) there were 56 GI complaints out of 515 subjects (10.8%) versus 61 out of 442 in the usually casein-containing control arms (13.8%). In the cross-over trials of soy protein supplements (Table 83) the same numbers of subjects overall had GI complaints during both soy and control phases of the trials.

Overall, there were a larger number and higher rate of adverse events for the soy groups versus the controls, and there were slightly more withdrawals from the soy arms due to taste aversion. However, estimation of GI disturbances was hampered because categorization and reporting of adverse events varied widely among studies and no article used standardized definitions of serious adverse events. Some studies combined nausea and gastric pain, or constipation and gastric discomfort, or headache, flatulence, nausea, dizziness, and rash, while others limited reporting to “GI disturbances” or “GI side effects.”

Of note, 1 case control study by Gunn 1980 from Los Angeles reported an outbreak of 508 afebrile GI illnesses in 1976 associated with consumption of a commercially marketed soy protein extender used in tunafish salad.[234] Extensive laboratory testing failed to identify any biological, chemical, or toxic agent. Significantly more cases than controls had a history of allergy ($P<0.02$). The authors concluded that consumption of textured soy protein may cause adverse GI symptoms in a small number of individuals.

Menstrual Complaints

Menstrual complaints included breast tenderness and other breast disorders, spotting (menses-like bleeding), other urogenital complaints, such as urinary tract or vaginal infections, and hot flashes. These complaints occurred in 15 of the 43 comparison studies, especially in the isoflavone (genistein 54 g/d) trials in post-menopausal women, but in none of the cohorts. In the 12 isoflavone trials (Table 80) there were, in total, 13 menstrual complaints in the isoflavone interventions versus 6 with controls. The control arms often included hormone therapy regimens such as estrogen/progestin therapy, but adverse events associated with these treatments are not recorded; hence the numbers for menstrual complaints in these parallel trials cannot be compared. In the 13 soy diet and beverage trials (Table 81) there were 2 menstrual complaints in the soy arms versus 1 in the control arms. In the 16 soy protein randomized parallel trials (Table 82) there were 20 menstrual complaints in the soy arms versus 19 in the controls. No subjects had menstrual complaints in the cross-over studies of soy protein supplements (Table 83).

Other Adverse Events

No study reported death or life-threatening illness associated with soy intake.

Other adverse events that were commonly reported included headache, dizziness, musculoskeletal complaints, weight gain, and rashes. Definitions for these observed adverse events were seldom provided. In addition, adverse event rates were reported frequently as a number or sometimes as a percentage of patients with symptoms. In some studies, adverse events were reported without differentiating by treatment assignment. Other studies did not report adverse events in specific patients who withdrew from the studies.

Other Reports

Three safety/pharmacokinetics articles on purified soy isoflavones were identified (Table 85). They generally concluded that dietary supplements administered as single doses that exceeded normal dietary intake by many-fold results in minimal clinical toxicity. These studies were performed in healthy males, males with prostate or colon cancer, and post-menopausal women.

Drug Interactions

Five studies reported serious interactions with concurrent medications: 2 interfering with warfarin, 1 with levothyroxine, 1 with oral contraceptives, and 1 with hormone replacement therapy.

In a case report, Cambria-Kiely 2002[235] observed a 70 year old man with atrial fibrillation who was stable on warfarin therapy 3 mg per day who developed subtherapeutic international normalized ratio (INR) values after ingesting soy milk. In a case series, Gaddi 1991[236] observed 10 hypercholesterolemic patients who were treated with different doses of warfarin after by-pass surgery. After 4 weeks of a soy protein diet there was a marked increase in all patients of prothrombin time: a mean increase of 114% after 2 weeks and a further increase of 2.6% during the next 2 weeks.

In a case report, Bell 2001[237] observed a 45 year old woman who had hyperthyroidism after a near-total thyroidectomy and radioactive iodine ablative therapy for papillary carcinoma of the thyroid. Routine “soy cocktail” protein supplements caused decreased absorption of levothyroxine.

Martini 1999[176] reported that 1 oral contraceptive user withdrew from a trial because, despite reporting regular periods before entry to the study, she had highly irregular periods while on the study.

In a safety and pharmacokinetics study involving 24 healthy post-menopausal women, Bloedon 2002[230] observed in the 8 women on hormone replacement therapy a mean increase of 30.4 U/L in lipase on day 3 after treatment with isoflavones, whereas lipase among the 16 subjects not on hormones had a mean decrease of 5.2 on day 3 (P=0.005). No other statistically significant dose-response effects were seen.

Table 80. Randomized trials that reported adverse events associated with consumption of soy isoflavones (without soy protein)

Author Year	Soy Isoflavones		Control		Duration (weeks)	Menstrual Complaints		GI Complaints		Withdraw Due to AE		Other Adverse Events
	N	Description	N	Description		Soy	Ctrl	Soy	Ctrl	Soy	Ctrl	
Parallel Trials												
Chen 2003	68	Isoflavones (80 mg/d)	67	placebo	52	9 (both groups)		20 (both groups)				Headache, bone or joint pain, hand itch, stomach tumor
	68	Isoflavones (40 mg/d)										
Maskarinec 2002	15	Isoflavones 100 mg/d	15	placebo	52			3	2	0	0	Isoflavones group: 4 headache/ dizziness Control: 1 headache/ dizziness, 1 breast cancer diagnosis
Morabito 2002	30	Genistein 54 mg/d	30	placebo	52	4	2					
Squadrito 2003	30	Genistein 54 mg/d	26	placebo	52	4	2					
Squadrito 2002	30	Genistein 54 mg/d	26	placebo	24	2						Genistein:1 vertigo Control: 1 vertigo, 2 parasthesia
Petri 2004	25	Soy germ 500 mg/d (Isoflavones 60 mg/d)	25	placebo	26	2	1	7	2	0	0	
Han 2002	40	Isoflavones 100 mg/d	40	placebo	16			1 (unclear which group)		2 (both groups)		
Secreto 2004	65	Isoflavones (80 mg/d) + melatonin	133	Placebo or melatonin	12	30 (menstrual spotting) (both groups)		frequent (both groups)		5	7	Tachycardia, weight gain, insomnia, and drowsiness/head-ache
	64	Isoflavones 40 mg/d										
Upmalis 2000	59	Isoflavones (50 mg/d)	63	placebo	12					1		Soy group: 1 urinary infection; placebo: 1 mastodynia. 30/89 reported 70 AEs; Placebo, 39/86 reported 79 AEs
Kumar 2002	33	Genistein 40 mg/d	33	placebo	12			4	4	4	2	Control group: 3 weight gain
Cross-over Trials												
Nikander 2004 15240647	28	Isoflavones (114 mg/d)		Placebo	12		1	2		2	1	Cross-over trial: 12 wks IF, 8 wks washout, 12 wks placebo. Dropouts occurred during 1st phase at 8 wks
Simons 2000	20	Isoflavones (80 mg/d)		Placebo	8	1			1 chole-cystitis			Cross-over trial: 8 wks IF, 8 wks washout, 8 wks placebo. Isoflavones group:1 parasthesia Control:1 parasthesia, 1 head noises
TOTAL	575		514			13	6	16	9	12	10	

Table 81. Randomized trials that reported adverse events associated with consumption of soy diets and beverages

Author Year	Soy Diets / Beverages		Control		Duration (weeks)	Menstrual Complaints		GI Complaints		Withdraw Due to AE		Other Adverse Events
	N	Description	N	Description		Soy	Ctrl	Soy	Ctrl	Soy	Ctrl	
Parallel Trials												
Maskarinec 2004	109	Soy foods (Isoflavones ~50 mg/d)	111	Control diet	104	ND		ND		ND		Total AEs reported: 37 upper respiatory, 12 musculo-skeletal, 8 menst-rual or GI, 4 head-ache or psycho-logical. 3 women in control during the trial, and 1 on soy afterwards were diagnosed with breast cancer
Lydeking-Olsen 2004	23	Soy milk 500 ml/d (Isoflavones 76 mg/d)+ progesterone	22	Progeste-rone	104	7 (both groups)		10	0	6	0	Additional soy AEs: 2 weight gain, 1 throat irritation.
	22	Soy milk 500 ml/d (Isoflavones 76 mg/d)	22	Placebo								
Chiechi 2002 11836040	58	Soy diet (Isoflavones ~40-60 mg/d)	55	Control diet	24	2	1			1		
Allison 2003	37	ISP (5 ScanDiet shakes/d)	37	1200 kcal diet	12			4 (both groups)		5 (both groups)		No serious AEs, but rates of gas or indigestion for soy shakes significant at $P<0.001$ at 4 & 8 weeks
Verrillo 1985	50	Soy beverage Cholsoy (60 g/d) as diet or supplement			16			1		1		
Knight 2001	9	Soy beverage TakeCare 60g/d (Isoflavones 134 mg/d)	11	Casein beverage	12			9 (both groups)		3	1	Soy total 9 AEs, placebo 12
Puska 2004	69	Soy Yogurt (41.4 g/d)	74	Placebo Yogurt	8			14	3	14	3	Reason for withdrawal was "refusal to take more" or AEs Symptoms however were mild

continued.

Table 81. Continued.

Author Year	Soy Diets / Beverages		Control		Duration (weeks)	Menstrual Complaints		GI Complaints		Withdraw Due to AE		Other Adverse Events
	N	Description	N	Description		Soy	Ctrl	Soy	Ctrl	Soy	Ctrl	
Parallel Trials												
Shorey 1981	14	Soy protein diet	13	Animal protein diet	6							initial increased fecal bulk and flatulence
Rossi 2000	10	Soy beverage (protein 40 g/d genistein 44mg/d)	10	Whey	3			"few" (both groups)				
Cross-over Trials												
Maki 2002	50	Soy beverage with calcium, vitamins C, D, K and isoflavones Optimize		$CaCO_3$ tablet	12							Total AEs: 16, mostly flu-like symptoms
Sirtori 1977	6	Soybean textured protein diet		"standard low lipid, low cholesterol diet"	3			1		1		
Schweizer 1983	6	Non-purified soya pulp (fiber 21 g/d) Purified soya fiber (fiber 21 g/d)			6			4				
Sirtori 1985	65	Textured soy proteins replace all animal proteins Textured soy proteins replace 50% animal proteins			8			Occa-sional & minor				
TOTAL	528		466			2	1	30	3	26	4	

Table 82. Randomized parallel trials that reported adverse events associated with consumption of soy protein supplements

Author Year	Soy Supplements		Control		Duration (weeks)	Menstrual Complaints		GI Complaints		Withdraw Due to AE		Other Adverse Events
	N	Description	N	Description		Soy	Ctrl	Soy	Ctrl	Soy	Ctrl	
Kreijkamp-Kaspers 2004	100	Soy protein 26 g/d (Isoflavones 99 mg/d)	102	Total milk protein	52	16	16	7	8	12	12	Total soy AEs: 253; 68 musculoskeletal 62 respiratory 29 dermatological Total control AEs:258; 70 musculoskeletal 70 respiratory 28 dermatological
Burke 2002	25	Phytoestrogen supplement 150 mg/d (Soy Isoflavones 120 mg/d) (also dong quai 100 mg, black cohosh 50 mg)	24	Placebo	24			1	3	0	0	Phytoestrogens: 1 pruritus
Murray 2003	16	ISP 25 g/d (Isoflavones 120 mg/d) + 2 doses of estradiol	14	whey and casein + 2 doses of estradiol	24	1	0	1	1	1	1	The abnormal uterine bleeding noted is due to endometrial polyp not detected at baseline. 2 other dropouts due to cervical stenosis (group unclear)
Teede 2001	105	ISP 40 g/d (Isoflavones 118 mg/d)	108	Casein	12	1		4	4	34 (both groups)		Soy arm: 2 weight gain
Albertazzi 1998	51	ISP 40 g/d	53	Casein	12			32	36	7	7	
Gardner 2001	64	ISP 42 g/d (Isoflavones 0 or 80 mg/d)	32	control	12	1		2	1	2	1	
Arjmandi 2003	20	Soy supplement 40 g/d (Isoflavones 88.4 mg/d)	22	Milk based protein	12			2	1	2	1	
Vigna 2000	51	ISP 60 g/d (Isoflavones 76 mg/d)	53	Casein	11.8	1	3	7	7	8	10	
Burke 2001	18	Soy protein supplement (high protein diet, high or low fiber) (66 g/d)	18	Low protein diet (high or low fiber)	8					3		Soy (high protein high fiber): 1 acute illness
Teixeira 2000	65	ISP 20-50 g/d (Isoflavones 33-95 mg/d)	16	Casein	6					8 (both groups)		2 of 8 dropouts in the 4 ISP groups described possible allergic reactions
TOTAL	515		442			20	19	56	61	35	32	

Table 83. Randomized cross-over trials that reported adverse events associated with consumption of soy protein supplements

Author Year	Soy Supplements		Control		Duration (weeks)	Menstrual Complaints		GI Complaints		Withdraw Due to AE		Other Adverse Events
	N	Description	N	Description		Soy	Ctrl	Soy	Ctrl	Soy	Ctrl	
Soy protein: Cross-overs												
Jayagopal 2002	32	Soy protein 30 g/d (Isoflavones 132 mg/d)		Cellulose	12			2	1	1	0	Soy group: 1 myocardial infarction; Control: 1 mouth ulcer
Teixeira 2004	14	ISP 0.5g/kg/d (Isoflavones 2 mg/d)		Casein	8			3	2			
Steinberg 2003	28	Soy protein 25 g/d (Isoflavones 107 mg/d) / Soy protein 25 g/d (Isoflavones 2 mg/d)		Total milk protein	6			2 (unclear which group)		6 (unclear which group)		
Blum 2003 12659466	24	Soy protein supplement 25 g/d (Isoflavones 85 mg/d)		Total milk protein	6			2	4	2	4	
Hermansen 2001	20	ISP 50 g/d (Isoflavones >165 mg/d)		Casein + cellulose	6			1		1	1	Soy: 1 unrecognized brain metastases, 1 liver metastases. Control group: 1 headache
Cuevas 2003	18	ISP 40 g/d (Isoflavones 80 mg/d)		Caseinate	4			6	7			
TOTAL	136					0	0	14	14	4	5	

Table 84. Adverse events reported in non-randomized studies (cohorts) of soy

Author Year	N	Soy Product	Duration (weeks)	Menstrual complaints	GI complaints	With-draw due to AE	Other Adverse Events
Medic Ristic 2003	106	Soy powder 20 g/d (7% lecithin, 17% soy protein)	24			5	headache, flatulence, nausea, rash
DeVere White 2004	52	Novasoy 5 g/d (Genistein 450 mg/d + other Iso 450 mg/d)	24		3		
Scheiber 2001	42	Whole soy food (Isoflavones 60 mg/d)	12		2		
Foth 2003	16	Soy protein 20 g/d (Isoflavones 20 mg/d)	24		2		
Pesciatini 1985	13	Soy based diet	8		1		

Table 85. Adverse events reported in safety/pharmacokinetics studies of soy

Author Year	n	Soy (Type, Dose)	Duration (weeks)	Adverse Events	Withdraw due to AE	Comments
Busby 2002	30	Genistein 1 dose (2, 4, 8 or 16 mg/kg body weight)	4	AEs include for 2 mg/kg group: 1 lipase, 1 amylase. For 4 mg/kg: loss of appetite, hypophosphatemia, pedal edema. For 8 mg/kg: loss of appetite, lipase, 3 cases hypophosphatemia, abdominal tenderness. For 16 mg/kg: leukopenia		Safety and pharmacokinetics in healthy men. Isoflavones higher than usually administered
Bloedon 2002	24	Genistein 1 dose (2, 4, 8 or 16 mg/kg body weight)	4	AEs include for 2 mg/kg group: 1 pedal edema; for 8 mg/kg: 1 nausea; for 16 mg/kg: 1 pedal edema, 1 breast tenderness		Safety and pharmacokinetics in post-menopausal women: Isoflavones higher than usually administered.
Takimoto 2003	12	Genistein 1 dose (2, 4, or 8 mg/kg body weight)	6	1 macropapular rash on extremities and face		Safety and pharmacokinetics in males with prostate or colon cancer. Isoflavones higher than in food.

Table 86. Randomized trials of soy that reported no adverse events

Author, Year	N	Soy (g/d)	Duration (Weeks)
Dragan 1992	38	Supro Soy beverage	8
Puska 2002	30	Abacor (soy protein 26 g/d) (Isoflavones 4 mg/d)	6
Crisafulli 2004	30	Genistein 54 mg/d	52
Alekel 2000	24	Isoflavone-rich soy (Isoflavones 80 mg/d)	24
Persky 2002	23	Isolated soy protein (Isoflavones 90 mg/d)	24
Sirtori 1999	21	Soya drink 35 g/d	4
Sirtori 2002	20	Soya milk 35 g/d	4
Anderson 2002	15	Isolated soy protein (Isoflavones 90 mg/d)	52
Uesugi 2002	12	Soy Isoflavone extract (Isoflavones 62 mg/d)	4
Shige 1998	11	Isolated soy protein 20 g/d	3
Total	**224**		

AE= Adverse Events; C=Control; ND= No data; nRCT= non randomized trial
GI includes nausea, bloating, flatulence, diarrhea, abdominal distension, constipation
Menstrual includes breast disorders, spotting (menses-like bleeding), other urogenital complaints, such as urinary tract or vaginal infections, and hot flashes

Chapter 4. Discussion

Overview

Many health benefits have been attributed to soy. Mechanisms that have been proposed for the effects of soy in promoting health include: estrogenic and anti-estrogenic effects, and antioxidant and cancer-enzyme inhibitor properties. Many studies have been conducted investigating the effects of a variety of soy products and soy foods on a range of health conditions. We summarized the results of these studies in this report.

We identified 4,471 potentially relevant citations and retrieved 599 full articles based on screening of abstracts, of which 178 clinical trials were included in this report. A little over half of all the studies were cross-over trials. Eight additional studies not analyzed for health effects were included in the analysis of adverse events associated with soy intake. Health conditions considered in this report include: cardiovascular, menopausal symptoms, endocrine function and menstrual cycle length, cancer and tumor related biomarkers, bone, kidney function, neurocognitive function, and glucose metabolism. Several of these conditions have multiple endpoints. The cardiovascular topic included the largest number of studies that evaluated low and high density lipoproteins (LDL and HDL), triglycerides, lipoprotein(a) [Lp(a)], blood pressure (BP), C reactive protein (CRP), homocysteine, endothelial function, systemic arterial compliance, and oxidized LDL. Altogether, about 40 endpoints or clinical outcomes were summarized in this report. We performed meta-analyses on several cardiovascular endpoints because these topics have a large number of available studies. However, for most other health conditions, the heterogeneity of the types of interventions and outcomes precluded meta-analysis.

The study quality was generally fair to poor. Overall, less than 5% of the studies were rated to be good quality (A), about 40% were rated to be fair quality (B), and about 55% were rated to be poor quality (C). Also, among the fair quality studies, about 5% reported data sufficiently poorly for particular secondary outcomes that study quality was downgraded for these outcomes. Among the common reasons that studies were rated fair quality were small sample size (less than 30 subjects consuming soy, unclear reporting regarding subject dropouts or somewhat high dropout rates (approximately 10-20%), incomplete reporting regarding soy composition or control, data reported only in figures, and minor discrepancies between text, tables, and/or figures. One-third of the poor quality studies were either uncontrolled, single cohort studies, non-randomized comparative studies, or comparative studies that were unclear whether they were randomized. Another third of the poor quality studies had dropout rates that exceeded 20%, including studies with over a 50% dropout rate, or unequal dropout rates between soy and control. Among other reasons studies were graded poor quality were lack of reporting of baseline data (i.e., initial level of outcome measure), inadequate accounting of important confounders (e.g., major differences in fat and protein consumption between study arms, medication use that affects outcomes), major discrepancies between text, tables, and/or figures or irreconcilable data that indicate likely improper statistical analysis, and substantial missing data.

Main Findings

Soy products

Soy supplements were used in about three quarters of all the trials analyzed in this report; soy foods were used in the remaining trials. In this report, soy milk/drinks were categorized as soy supplement. Fifty-seven percent of the soy supplement trials used soy protein with isoflavones, 36% used isoflavones alone, and 6% as soy protein without isoflavones. In about one-half of the soy foods trials, textured soy protein was used. Soy flour was used in about one-quarter of the soy foods trials. There are 146 separate treatment arms of soy supplementations and 68 separate treatment arms of soy foods or diets. The total isoflavones range from 0 mg to 185 mg per day. The total protein intake from soy ranges from 0 g to 154 g per day. The average study evaluated a large quantity of soy product. The median soy protein dose is 36 g per day, equivalent to over a pound of typical tofu or 3 typical soy shakes per day. Also of note is that most studies were of relatively short duration. Approximately half the studies were shorter than 12 weeks and one-third shorter than 6 weeks. With few exceptions, though, studies of less than 4 weeks' duration were excluded.

Overall Effects

Meta-analysis revealed a statistically significant reduction of LDL and triglycerides across a heterogeneous range of soy interventions, but no effect on HDL or BP. Meta-regression suggested a possible association between soy protein dose and LDL reduction, but no dose-response for soy isoflavones for any lipids or BP. However, the few studies that directly compared different types and doses of soy products did not consistently find a soy protein dose effect.

Some evidence suggests that soy isoflavone supplements may reduce menopausal symptoms in post-menopausal women. Other soy products did not show an effect, and the evidence does not support a benefit of soy products for peri-menopausal women or women undergoing breast cancer chemotherapy.

Overall, studies have found no benefit of soy products on other evaluated CVD risk factors, endocrine function, tumor biomarkers, bone health, or other evaluated conditions. However, no study evaluated clinical outcomes for cardiovascular disease, endocrine disease, cancer incidence, or osteoporosis. Furthermore, heterogeneity of soy products, comparators and populations, along with often poor study quality and frequent small numbers of studies hampered definitive evaluation of the effect of soy products.

Among studies that reported adverse events, the overall frequency of adverse events in subjects consuming soy was similar to that of subjects in control arms. However, gastrointestinal complaints were substantially higher among subjects consuming soy. Menstrual complaints were also higher among post-menopausal women consuming isoflavone supplements. Adverse events were almost universally minor.

Cardiovascular Endpoints

A total of 68 randomized studies reported data on total cholesterol, LDL, HDL, and/or triglycerides. The total isoflavones range from 0 mg to 185 mg per day, with a median of 80 mg. The total protein intake from soy ranges from 14 to 113 g per day, with a median of 36 g. There is a great deal of heterogeneity of effects found on lipoprotein and triglyceride levels. Overall, the majority of studies reported small to moderate effects on the lipids, despite a wide range of

net effects for total cholesterol, LDL, and triglycerides. Sixty-one studies reported data on the effect of consumption of soy products on total cholesterol levels. The median net change compared to control found was approximately 6 mg/dL decrease (2.5%). A meta-analysis of 52 studies that reported data on the effect of soy consumption on LDL levels yielded a statistically, though not clinically, significant net decrease of 5 mg/dL (approximately 3%). A meta-analysis of 56 studies that reported data on the effect of soy consumption on HDL levels found a non-significant net increase of less than 1 mg/dL. A meta-analysis combining 54 studies that reported data on the effect of soy consumption on triglyceride levels yielded a statistically significant net decrease of 8 mg/dL (approximately 6%). These small benefits to lipid levels may have a debatable benefit in individuals to reduce the risk of clinical cardiovascular disease (CVD), though on a population level – assuming that a whole population increased its soy consumption – these lipid changes could possibly have a substantial effect on incidence of CVD.

However, the majority of studies used large doses of soy equivalent to over a pound of tofu or over 3 servings of a typical soy protein shake daily. Across studies there is some indication that increasing doses of soy protein may be associated with increasing LDL benefit, although this effect is statistically significant only from studies with elevated mean baseline LDL and only if studies with marginal amounts of soy protein are also included. No association was found between soy protein dose and effect on either HDL or triglycerides, or between soy isoflavone dose and effect on any lipid. Studies that investigated possible dose effects generally also found no association.

A total of 22 studies reported data on the effect of consumption of soy products on systolic and diastolic BP. Meta-analysis of blood pressure (BP) found no effect of soy consumption. The net effect on systolic BP was –1 (95% CI –3, +1) mm Hg, and on diastolic BP –1, (–2, +0) mm Hg. No association was found between baseline BP, soy protein or isoflavone dose and effect on BP.

Some of the well known emerging risk factors for CVD included for analysis in this report are: Lp(a), CRP, homocysteine, endothelial function, systemic arterial compliance, oxidized LDL. The total number of studies that reported data on the effect of soy consumption are: 18 studies on Lp(a), 3 on CRP, 5 on homocysteine, 10 on endothelial function, 3 on systemic arterial compliance, and 13 on oxidized LDL. Across these studies, there is no discernable effect based on the type of soy products. Majority of studies were of poor quality with a narrow range of applicability. Given the limited evidence and poor quality studies, no conclusions could be drawn on the beneficial or harmful effects of consumption of soy protein on these (non-lipid, non-BP) putative risk factors for CVD.

Menopausal Symptoms

A total of 21 trials examine the effects of soy and/or its isoflavones on hot flashes and night sweats in women. These trials generally measured frequency and severity of the symptoms. However, a large number of vasomotor symptom scores or indexes that employed a variety of frequency intervals were used by the investigators. These factors made meta-analyses unsuitable and limited the comparisons of results across studies. Furthermore, many of the studies had high withdrawal or dropout rates that were frequently uneven between soy treatment and control arm; this further limits the validity of these clinical trials. Overall, soy isoflavones supplements might reduce hot flashes in symptomatic post-menopausal women, compared to the placebo. Among the 6 randomized trials showing the positive results, the net reduction in weekly hot flash frequency ranges from 7% to 40%. However, these trials are mostly low quality due to high

dropout rates. No significant effect was found for soy and/or its isoflavones treatments compared to the control treatments on vasomotor symptoms in peri-menopausal women or women who had breast cancer therapies.

Endocrine Function

Forty-seven papers included endocrine measurements as primary or secondary endpoints. Testosterone was an outcome of clinical importance both as a risk factor for cancer and as part of the initial evaluation of male infertility. Five studies with a total of 179 participants reported testosterone levels in healthy males before and after soy consumption. Four out of the five studies found a non-significant decrease in testosterone levels. The small total number of subjects as well as the low quality of these studies precluded any meaningful conclusion. Follicle stimulating hormone (FSH) level is measured at the initial evaluation of male and female infertility. Results were conflicting and no significant effect was found.

Twelve studies reported estradiol levels in 434 pre-menopausal women. The overall effect of soy on estradiol levels was not consistent. Most of the studies showed a trend for soy in reducing estradiol, although they failed to demonstrate a significant effect. Six randomized trials reported the effect of soy on thyroid stimulating hormone (TSH). No overall effect of soy on TSH and thyroid function is clear.

A total of 11 trials in 10 publications evaluated the effect of soy on menstrual cycle length in pre-menopausal women. A wide range of soy interventions was used in these trials made a conclusion of the effects from soy difficult, because of the limited number of studies in each comparison category. These trials did not show significant changes in menstrual cycle length after treatments of soy and/or its isoflavones.

Cancer and Tumor-Related Biomarkers

Twenty-four studies evaluated subjects without a history of cancer for effects of soy on tumor-related biomarkers. None of the trials reported the development of cancer as the outcome. Most studies measured the effect of soy on estrogens and estrogen metabolites as well as on estrogenicity indicators. There were also trials, which aimed at correlating soy with other possible cellular pathways of cancer prevention. No causal relationship could be actually established between these markers and cancer because they do not represent risk factors for cancer disease. Only 2 studies reported on testosterone levels, which is a risk factor for prostate cancer, as an endpoint.

Bone Endpoints

A total of 26 studies were included in this section. Ten trials examined the effects of soy and/or its isoflavones on bone mineral density and/or bone mineral contents, and 22 trials examined the effects of soy and/or its isoflavones on bone biomarkers related to bone turnover or bone remodeling. There were few randomized trials of long-term duration and a wide variety of soy interventions were used across studies, therefore it is difficult to draw reliable conclusions about the effects of soy on bone endpoints. No consistent effect was found between soy protein with isoflavones and that of isolated soy protein without isoflavones.

Nine studies each reported data on the effects of soy on bone formation markers, serum osteocalcin (OC) and bone specific alkaline phosphatase (bAP), respectively. The majority of these trials enrolled pre- and post-menopausal women. No significant effect was reported by most of the studies.

In the studies that evaluated bone resorption biomarkers, 2 randomized trials of urinary hydroxyproline in post-menopausal women reported no significant differences between soy protein with isoflavones diets, and the control diets. There is no consistent effect of soy protein and/or its isoflavones on urinary cross-linked N-telopeptide (NTx) levels when compared to the control treatments in both pre-menopausal and post-menopausal women.

Only a single study of genistein found consistently statistically significant benefits of soy consumption on measures of bone health.

Neurocognitive and Kidney Functions, and Glucose Metabolism

Four studies examined the effects of soy on cognitive function of post-menopausal women and college students of both sex. Overall, no significant consistent effect on neurocognitive functions such as verbal episodic memory was noted. Only 1 small study in patients with type 2 diabetes assessed the effect of soy on kidney function. No significant changes in glomerular filtration rate as seen after 8 weeks of soy protein diet. Six studies evaluated the effect of soy on fasting blood glucose. No significant changes were reported.

Adverse Effects

Overall, the numbers and rates of adverse events reported were similar between the soy treatment arms and their respective controls (151 vs 113, 8.6% vs 7.2%). However there were no differences according to the types of soy consumed.

The most frequently reported adverse events among a total of 3,518 subjects in 49 trials that reported adverse events were gastrointestinal in nature, reported in 30 of 41 comparison studies of soy diets and beverages, soy proteins, isoflavones, and phytoestrogen supplements. Mostly the gastrointestinal complaints were reported in soy diet and soy protein trials. The amount of soy protein in these trials ranged from 20 to 60 g/day, but there was no clear dose relationship. In the comparison trials of purified isoflavone interventions as well as soy diets and beverages, there were more gastrointestinal complaints (46 vs 12). Overall, there were 116 complaints in the soy arms, compared to the controls. Menstrual complaints were also common, reported in 15 studies , especially in those 12 that used purified isoflavone in dosages ranging from 40 to 100 mg/day (13 adverse events vs 6), but overall, in all types of soy consumption, the numbers of adverse menstrual events were 35 versus 26 in soy arms and controls, respectively. The majority of these patients were post-menopausal women, and the controls frequently included hormone therapy regimens. Other adverse events included musculoskeletal complaints, headache, dizziness, and rashes. There were also more withdrawals from the soy arms due to aversion of taste.

Limitations

Despite the large number of trials that have been performed, the health effects of soy for many conditions that have been studied remain uncertain. The methodological quality of many studies evaluated in this report was poor (Grade C). There was great heterogeneity among studies, particularly among the interventions analyzed. Comparisons across the myriad types of soy are intrinsically very difficult. This difficulty was compounded by the use of soy as both a supplement and as an integral part of the diet; furthermore for numerous studies, it is difficult to distinguish between supplement and diet. It is likely that studies of supplements and diet are not easily comparable. Most studies also involved a small number of study subjects and were of

short duration. The universal issue of possible publication bias, where negative studies are less likely to be published and are more likely to be published later, is a potential concern. However, for most outcomes, the majority of studies reported negative outcomes, and there was no obvious evidence of publication bias among the lipid studies (where there is evidence of a positive effect).

Most of the studies evaluated the effects of soy on various biomarkers or measures, not clinical outcomes. Several of these endpoints evaluated in the studies, such as BP, LDL-cholesterol, and bone mineral density, do have meaningful correlations with clinical outcomes. Cardiovascular endpoints were assessed by the largest number of studies. Overall, soy was found to have only a small effect on lipids. However, the duration of these studies were generally short, and it is uncertain whether the results would be sustained. Few studies directly compared soy products, mostly comparing soy protein with varying amounts of soy isoflavones. Only one study, Lichtenstein 2002 [56] performed a factorial design study comparing both present and absent soy protein and present and absent soy isoflavones, thus allowing analysis of both the effect of soy protein and soy product.

Reduction of hot flashes by soy was seen in trials involving post-menopausal women. Most of the trials lasted only 3 to 4 months, thus their long-term benefits remain unclear. In addition, different measurements were used to assess benefits across studies thus making comparisons and synthesis difficult. Soy phytoestrogens are seen by some as an alternative to estrogen replacement therapy to treat post-menopausal symptoms. However, the estrogenic effect of soy in potentially promoting tumor recurrence raises the concern for its use by breast cancer survivors. The current literature provides no data to address this issue. It remains unclear whether there is a real hormonal effect of isoflavones in women or men, either on hormone levels or hormonal effects; this could be a subject of future research.

Some of the conditions and outcomes were evaluated by only a few studies. The question of whether long-term consumption of soy impairs neurocognitive function cannot be answered with the current data.

Future Research

This report dealt with a broad range of health conditions and endpoints, thus it is difficult to focus research recommendations on a specific area. Common to most bodies of evidence regarding medical fields, better quality, well-reported, larger and longer duration studies are needed to address the questions of interest.

It is generally very difficult to evaluate different effects due to different products or in different populations when these differences can be found only across studies. Additional studies are needed that directly compare different doses and types of soy products, and that perform appropriate sub-group analyses such as by sex or age or baseline risk.

Given the complexity of food products, it is particularly important that future studies of soy products (and all food products) report complete and thorough descriptions of the products under investigation. In the case of soy, this includes quantity (and possibly type) of soy protein, quantity and type of isoflavones, and quantity and type of other constituents of the soy product that may exert an effect.

Since the evidence does not strongly suggest a dose-response for either soy protein or isoflavones, it may be appropriate to investigate other soy constituents as possible active factors.

Consideration (and full reporting) is needed of what foods are being replaced by the consumption of the soy products (whether they be used as part of the diet or as supplements) and this needs to be controlled for. This includes care being taken that appropriate controls are used. Otherwise, interpretation of the study can be fraught with difficulties. It should be clear that the comparison is between soy and an alternative, not, for example, low-fat versus high-fat diets, high-protein versus low protein diets, or plant versus animal protein diets.

We strongly recommend that all future randomized trials – including those of soy and other nutritional products – use the CONSORT statement as a guide to reporting (http://www.consort-statement.org).[238,239] This will not only improve the readers' understanding of the trials, but should also improve the quality of published studies. About 10% of studies on soy products failed to adequately report that they were randomized; many studies failed to completely and accurately report their data, including baseline data, numbers of subjects, numbers of dropouts, and statistical methods used; and over 20% of studies had very high dropout rates, from 20% to more than 50%. These are examples of issues that could be greatly improved by conscientious adherence to proper study design and reporting.

While we reviewers of the evidence are not in a position to make specific recommendations about how research in the field of nutrition should fundamentally change, we offer the following observations for consideration by experts in nutrition research when planning future research. We suggest that these issues be discussed at future workshops that either plan future studies or review the needs of future food-related research. Examples of these include the working group on future clinical research directions on omega-3 fatty acids and CVD, convened by the Office of Dietary Supplements and the National Heart, Lung, and Blood Institute on June 2, 2004 in Bethesda, MD (www.nhlbi.nih.gov/meetings/workshops/omega-3/omega-3-rpt.htm, accessed April 28, 2005) and the workshop "Assessing the Health Effects of Bioactive Food Components" sponsored by the Office of Dietary Supplements and held in conjunction with the Experimental Biology 2005 meeting in San Diego).

Conducting clinical trials in the area of health effects of food substance is fraught with difficulties. There is a complex interplay among the various components and potentially active substances within the foods and with other foods, dietary variations, as well as with other lifestyle and clinical variations among individuals. Controlling for these factors is difficult within a trial. Interpreting discrepant results among trials is even more difficult. Isoflavones are believed to be the key active substance in soy, but this is by no means certain. Little data suggest that the amount of soy isoflavones is associated with an incremental effect and studies of soy protein with little or no isoflavones frequently had similar effects as isoflavone studies. It may be that neither soy protein nor soy isoflavones are the active component of soy. No studies that we reviewed examined this possibility. Nevertheless, difficulties with attempting to ascribe a food health benefit to a specific component of the food are highlighted by the recent spate of disappointing results from antioxidant trials, which suggest that the evaluation of potential nutrient benefits may need a paradigm different from the traditional clinical trial model.

The bioavailability of an ingested nutrient may also be an important factor in the determination of the beneficial effect. Several factors may affect the bioavailability of ingested nutrients: 1) absorption rate, affected by the interactions with competitive nutrients, the usual diet compositions, and types of foods or supplements; 2) incorporation rate into the blood stream, in which complex mechanisms might be involved, such as the functions of facilitated transporters, receptors on the membrane, or cellular binding proteins; 3) metabolism of the intestinal bacterial environment. Any one of these factors alone does not determine the

bioavailability. In order to gain insights on the question of dose-response relationship, we not only need the information on the soy isoflavone contents, including types and amount, but also on the bioavailability of the ingested soy isoflavones.

Unfortunately studies that attempt to control for the myriad factors that interfere with clear interpretation of the effect of food products such as soy tend to be highly artificial, with little applicability to the average person. Clarity is needed to define what study questions are of interest. Metabolic laboratory studies or investigations of highly structured or restricted diets (such as those where soy protein constitutes the bulk of daily protein consumption) are of potential value only to possibly determine which components of soy are bioactive or to determine what extremes of diet may be necessary to achieve a benefit. Studies that substitute practical amounts of soy products into average people's diets would better address the question of whether people should make the effort to include more soy in their diets, but these studies will invariably be difficult to interpret. An exception to this may be studies of soy isoflavone supplements (e.g., non-food capsules), which may be interpreted more like usual drug trials.

Carefully controlled efficacy studies (those conducted under the artificial conditions of a clinical trial) may still be useful to pin down the relative effects of various components of soy. Once this is better clarified, more practical effectiveness studies (that aim to test the value of an intervention in more real-world scenarios) with feasible interventions might be more important.

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Abbreviations

Abbreviation	Description
Quality Score: A	Good quality study, least susceptible to bias. See Chapter 2, Methods.
Quality Score: B	Fair quality study, more susceptible to bias. See Chapter 2, Methods.
Quality Score: C	Poor quality study, most susceptible to bias. See Chapter 2, Methods.
🚹🚺	Broadly applicable study (referable to population category)
🚹🚺	Moderately applicable study (referable to population category)
🚹	Narrowly applicable study (referable to population category)
♀	Women (all)
♂	Men
5-OHmdU	5-Hydroxymethyl-2'-deoxyuridine
apo(a)	Apolipoprotein(a)
apoB-100	Apolipoprotein B-100
AHRQ	Agency for Healthcare Research and Quality
ASVD	Atherosclerotic vascular disease
bAP	Bone-specific alkaline phosphatase (serum)
BMC	Bone mineral content
BMD	Bone mineral density
BP	Blood pressure
Breast CA	History of breast cancer
CAB	Commonwealth Agricultural Bureau (database)
CI	Confidence Interval
CKD	Chronic kidney disease
CRP	C-reactive protein
CTx	C-telopeptide
CVD	Cardiovascular disease
d	Days
DC	Digit cancellation
DHEA	Dehydroepiandrosterone
DHEAS	Dehydroepiandrosterone sulfate
DHT	Dihydrotestosterone
DM	Diabetes mellitus
D-pyr	Deoxypyridinoline (urinary)
E2	Estradiol
EPC	Evidence-based Practice Center
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
FTI	Free thyroxine index
GI	Gastrointestinal

Abbreviation	Description
HDL	High density lipoprotein
HP	Hydroxyproline (urinary)
hs-CRP	High sensitivity CRP
HTN	Hypertension
IGF	Insulin-like growth factor
IGFBP-3	Insulin-like growth factor binding protein-3
Iso	Isoflavones
ISP	Isolated soy protein
LDL	Low density lipoprotein
LH	Luteinizing hormone
Lp(a)	Lipoprotein (a)
mo	Month(s)
N	Number of subjects
NCCAM	National Center for Complementary and Alternative Medicine
NCI	National Cancer Institute
nd	No data
NF-κB	Nuclear factor-κB
NIH	National Institutes of Health
NRCT	Non-randomized controlled trial
NS	Non-significant
NTx	Collagen type I cross linked N-telopeptide (urinary)
OC	Osteocalcin (serum)
P within	*P* value of within-cohort change
P btw Soy	*P* value of difference in effect between soy treatments
P vs Control	*P* value of effect compared to control (net change)
PDGF	Platelet-derived growth factor
peri♀	Peri-menopausal women
post♀	Post-menopausal women
pre♀	Pre-menopausal women
PSA	Prostate specific antigen
PTH	Parathyroid hormone
PTI	Protein Technology Institute, Inc
Pyr	Pyridinoline (urinary)
RCT	Randomized controlled trial (parallel design)
SE	Standard error
SHBG	Sex hormone-binding globulin
t	Text only, no data reported
T max	Time of maximal concentration
T. Isoflav	Total isoflavones

Abbreviation	Description
T3	Triiodothyronine
T4	Thyroxine
TBARs	Thiobarbituric acid reactive substances
TBG	Thyroid binding globulin
TEP	Technical expert panel
Tg	Triglycerides
TSH	Thyroid stimulating hormone
Tufts-NEMC	Tufts-New England Medical Center
UI	Unique Identifier (from MEDLINE, Used when multiple studies have the same first author and year)
w/	With
w/o	Without
WHO	World Health Organization
wk	Weeks
Xover	Cross-over studies (randomized)
yr	Year(s)

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